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Three-Parent Babies… Or Are They?

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Abstract
Considering the topic of 3-parent IVF, this paper aims to determine how much DNA, in terms of base pairs of nucleotides, is actually contributed by the notorious 'third parent'. By considering how much DNA is contained in the nucleus and mitochondria of an average cell, the percentage contributed by each parent to the recipient child is found to be 0.27% from the third parent, and 49.9% from each of the two conventional parents. An alternative calculation is also presented, using only the coding DNA region, however this is rationalised to be a less appropriate model.

Introduction
Due to the maternal inheritance of mitochondria, and their associated DNA, disorders of this organelle are always passed from a child's mother. The role of mitochondria within the majority of the body's cells is to essentially provide energy-rich molecules to be used in the cells activities. This means that mitochondrial disorders, whether confined to a single organ or body-wide, most commonly present with debilitating symptoms [1].

This outcome means, the knowledge that you were a carrier for one of these disorders may deter you from having children. A recent yes vote in parliament on a new technique which effectively replaces the conventional mother's mutated mitochondria with those of a 'second mother' has given a new option to potential mothers which carry mitochondrial disorders [2].

The offspring produced by this new procedure would contain only their conventional parents nuclear DNA, however the mitochondria, and its associated DNA usually provided by the mother would come from the second mother, or 'third parent'.

By discussing how many base-pairs (b.p's) of nucleotides (the building blocks of DNA) make up nucleic and mitochondrial DNA, it is possible to determine the percentage contribution of each parent to the child, in terms of how many base pairs they contribute to all those contained in the child's cells.

Base pairs in a human cell
The human genome, without mitochondria, contains approximately $3x10^9$ base pairs [3]. Whilst not all cells contain a nucleus i.e. red blood cells, the majority of cells within the body will contain all of these base pairs within a membrane-bound nucleus.

Similarly, not all cells throughout the body will contain mitochondria. However, cells which do contain mitochondria will have more than one, up to 2000 in the cells requiring the most energy i.e. cells within the liver [4]. For the purpose of this model an estimated average value of 500 mitochondria will be taken. As each contributes 16500 base pairs, a total of $8.25x10^6$ mitochondrial b.p.s will be present in the cell [5]. Therefore there will be a total of $3.008x10^9$ (4SF) b.p's of DNA within this model of a typical cell.

Contribution of each parent
Considering this typical cell, the contribution of each parent can be determined as the origin of the genetic information is decided. The premise of the procedure is that all mitochondria are donated by the second mother (3^{rd} Parent), therefore the $8.25x10^6$ b.p's from her will make up the following percentage of the whole cell.

$$3^{rd}Parent\ \% = \left(\frac{mitochondrial\ b.p's}{total\ b.p's}\right) \times 100$$

$$3^{rd}Parent\ \% = \left(\frac{8.25 \times 10^6}{3.008 \times 10^9}\right) \times 100 = 0.27\%$$

Whilst the contribution of the conventional father and mother is not equal even in typical fertilisation, on average a child will receive half its nucleic genetic information from each of these two individuals. As such the contribution in terms of percentage of base pairs is equal for each of these parents.

$$Conventional\ Parent\ \% = \left(\frac{\frac{1}{2}nucleic\ b.p's}{total\ b.p's}\right) \times 100$$

$$Conventional\ Parent\ \% = \left(\frac{1.5 \times 10^9}{3.008 \times 10^9}\right) \times 100$$

$$Conventional\ Parent\ \% = 49.9\%$$

Therefore of the child's total genetic information 0.27% is contributed by the third parent (second mother) and 49.9% by each of the original two parents. The combination of these values is more than 100% due to rounding.

Only the genes which are expressed?

One of the areas of controversy associated with this procedure is its likening to 'designer babies' where phenotypic traits such as eye colour are chosen by the parents. In this case, it may then be more appropriate to only consider the expressed 'coding' regions of the nucleic genome (exons), as these contribute to such traits. In this case, the number of nucleic base pairs is reduced to $9x10^7$ whilst the mitochondrial base pairs remains the same as the DNA of these organelles contains an insignificant amount of non-coding introns (intervening regions), so the contribution of mitochondrial base pairs will remain the same [6, 7]. Considering these adapted values, each parent contributes the following percentage to the child's expressed DNA

$$3^{rd}Parent\ \% = \left(\frac{mitochondrial\ b.p's(new)}{total\ b.p's(new)}\right) \times 100$$

$$3^{rd}Parent\ \% = \left(\frac{8.25 \times 10^6}{9.82 \times 10^7}\right) \times 100 = 8.40\%$$

$$Conventional\ Parent\ \% = \left(\frac{\frac{1}{2}nucleic\ b.p's(new)}{total\ b.p's(new)}\right) \times 100$$

$$3^{rd}Parent\ \% = \left(\frac{4.5 \times 10^7}{9.82 \times 10^7}\right) \times 100 = 45.8\%$$

However, whilst the genomic exons determine these phenotypic traits, it is regions of the adjoining introns which can control the expression of genes i.e. when and how much a gene should be transcribed [8]. Considering this, and that the function of all the non-coding regions are unknown, the previous percentages are a better representation of the contribution of each parent.

This second model also assumes that all the mitochondrial DNA contributes to the phenotype. However, it is not responsible for the phenotypic traits such as intelligence and eye colour which have caused debate about the procedure, another reason why the first model is a more suitable representation.

Conclusion

This simple model has determined the contribution of each of the three parents, showing that the contribution of the non-conventional 'second mother' is approximately 200 times smaller than either of the conventional parents. This contrasts published work suggesting a contribution of only 0.01% from the third parent, however the method used here considers the third parent's contribution to the whole percentage, rather than the percentage of difference in three-parent individuals [9].

This first model included is considered a better representation as it considers all DNA present in the cell, removing the need to draw a difficult line between what does and does not affect the phenotype of the recipient child. Extrapolation of the results to the entire body would produce the same result as an average value of mitochondrial DNA has been used, allowing a simple calculation to determine the contribution of each parent to the child.

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