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VIEWPOINT

Ethics of mitochondrial therapy for deafness

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Abstract

Mitochondrial therapy may provide the relief to many families with inherited mitochondrial diseases. However, it also has the potential for use in non-fatal disorders such as inherited mitochondrial deafness, providing an option for correction of the deafness using assisted reproductive technology. In this paper we discuss the potential for use in correcting mitochondrial deafness and consider some of the issues for the deaf community.

"How would that child feel about having genetic testing, how would that child feel about their parents actually considering changing part of them which might have been …it might become an integral part of them?"

The quote above was made during research into families with the lived experiences of heritable deafness and reproductive decision-making; it brings in to question the role of mitochondrial transfer in correcting genetic diseases associated with mitochondrial mutations.[1]

Whilst many of the inherited mitochondrial disorders are severe and life-threatening, deafness due to mutations in the mitochondrial genome are not necessarily life-threatening. This raises the question of whether attempts to modify the mitochondrial genome in deaf families with no other significant pathology is appropriate? Controversy surrounds deafness, as many in the deaf community do not consider it to be a disability, and thus, not in need of any correction, whilst others seek to use technology to overcome what is often perceived as a 'disability' with regard to employment prospects and schooling to avoid limited opportunity.[2]

In this viewpoint article we consider the potential issue of correcting a 'disability' (deafness), which has no other significant pathology.

A medical concept of disability is one that treats disability as a range of conditions, which limit an individual's ability to participate in the activities of a 'normal' society. The assumption is that impairment exists in the individual, something, which may not be assumed by the individuals themselves. Shakespeare discusses disability as a social construct rather than an outcome of medical incapacity.[3] This sociological perspective rejects the notion of 'fixing' by medical intervention and its accompanying external judgments of 'quality of life' for the disabled individual, which may be viewed as discriminatory.[4]

Families with hearing impairment (or being deaf) often do not necessarily see themselves as disadvantaged by a disability but instead simply displaying one more aspect of human diversity.[1,2] Thus deafness while annoying at times may be perceived more a disability in the hearing community. Clearly for some forms of deafness there are treatments/corrections such as hearing aids and cochlea implants but for many in the deaf communities sign language is the medium of communicating within their communities and considered as giving a sense of identity.[4]

Hearing loss has a diverse spectrum of causes from environmental effects to hereditary causes. Estimates vary regarding hereditary hearing loss however it appears to occur in approximately 1 in 2000 newborns with 50% of these being attributed to differing modes of inheritance[5] with more than 100 genes being identified as being associated with syndromic and non-syndromic deafness.[5–7] However up to 80% of mutations in the connexin 26 gene may be attributed to the 35delG mutation[8] causing disruption of recycling of potassium ions to the endolymph resulting in cellular dysfunction and ultimately cell death.[8]

Many other genes have now been identified associated with autosomal dominant and X-linked causes of deafness.[6] The ability to now identify genes associated with deafness further shifts 'deafness' in to a medicalised model rather than the social model.[6,9] Thus making it possible to not only identify the

cause of deafness but to also provide prenatal diagnosis and the possibility of predicting the individual characteristics of the deafness.

Many in the deaf communities are ambivalent about the genetic technology approach to deafness viewing it with distrust and having eugenic implications.[4,7,9] Some consider the medical genetic approach as a means of society eradicating the deaf culture built up over 200 years in a wide range of countries. However, there are many in the deaf community who view the changes as positive, having an answer to generations of family deafness, being able to prepare for the birth of a deaf child and the genetic knowledge offering the possibility of 'repair or cure' in the future.[7,10]

Mutations in the mitochondrial genome can affect the deafness in the general population in two ways: those that are present at birth (approximately 1% of children with pre-lingual deafness) and those mutations, which affect people, as they get older (presbyacusis).[6] Overall at least 5% of a Caucasian population will experience post-lingual non-syndromic hearing loss due to mitochondrial DNA mutations.[10–13] Despite the relatively small size of the mitochondrial genome (~16.5kb) at lease 50 mutations have been identified that will lead to either syndromic or non-syndromic hearing loss.[5,1]2

Approximately 25 mutations are associated with significant pathology in the individual relating to heart and liver failure, defects in energy metabolism, loss of motor skills and early death.[14,15] However, those mutations with no significant associated pathology may present with progressive sensorineural hearing loss, which may start in early childhood and have variable severity.[15] Understanding the linkage between the mutation causing deafness and the biochemical defect has been difficult although all mitochondrial genes are associated with either ATP generation (approximately 95% of all cellular energy), oxidative stress control and apoptosis and a strong relationship has been established with cochlear degeneration.[8,15]

Correction of deafness has had mixed success within the deaf community and there is certainly a division in the desirability of correcting deafness using 'genetic technologies'.[1,2,6] Will the possibility for pre-implantation correction for deafness change, however, with the advent of oocyte mitochondrial transfer? Thus providing the opportunity to 'correct' the mutation prior to embryo implantation and subsequent development rather than decisions on gene identification and deciding on fetal outcome later in pregnancy.[14]

Although the proposed use of mitochondrial transfer has been to correct those mitochondrial mutations with severe outcomes, it is clear that any readily identifiable mitochondrial mutation associated with deafness could also qualify for this technique. Is this different to selecting for deafness later in pregnancy? Would the resulting (hearing) child growing in a deaf family feel a product of cellular engineering, not-withstanding the issue associated with the three-parent association currently being debated.[13] Is this the "best possible child" and what safe guards can be considered for the identity of the child and an open future?[17,18] Can both the family and the child live with certainty that the 'correction' in early development will hold for the future or will there be forever a degree of uncertainty?[19]

As affected individuals are often heteroplastic, there is a threshold for the phenotypic expression of all mitochondrial disease, with increasing numbers mutant mitochondria progressing to the more serious pathology and outcomes.[14,20] In the situation for deafness how might any 'threshold' be tolerated given that the host oocyte or zygote may retain mutant mitochondria resulting from the transfer? Clearly if the therapy works then the child enters the 'hearing world' and may have different options to those experienced by its non-hearing siblings and parents. But would the 'biologically engineered child' consider that their rights to an open future to have been violated with no options on reproductive autonomy for females who will pass on their 'borrowed' mitochondria to the next generation. Alternatively the rights of males discovering that their germ-line mitochondria were ineffective in sperm motility thus rending them infertile?

The question must arise whether correcting a disability—either real or perceived (in the case of deafness)—not only removes the respect for difference but removes the future decision-making of health outcomes from the manipulated, *in-vitro* conceived child.

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