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Letter to the Editor

The Common 4977bp Mtdna Deletion Is Not Responsible For Infertility on In Vitro Fertilisation

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In a recent article, Mirabutalebi *et al.*, reported about a study of 52 females in whom two consecutive trials of in vitro fertilisations (IVFs) failed to result in a successful pregnancy (Mirabutalebi, S.H. *et al.*, 2018). Infertility in these females was attributed to the presence of an mtDNA deletion of 4977 basepairs (bp) in blood lymphocytes in 58% of the females >35 years of age and in 39% of the females <35 years of age (Mirabutalebi, S.H. *et al.*, 2018). Single mtDNA deletions usually manifest as mitochondrial disorders, such as Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia, Pearson syndrome, or non-specific multisystem disease, predominantly concerning the neurologist. We have the following comments and concerns.

The main shortcoming of the study is that the genetic tests were carried out on lymphocytes and not on oocytes, which can be regarded as the cell in which impaired mitochondrial functioning is expected. Since oocytes were available from these females the study should be repeated on oocytes to see if the frequency of the common 4977 bp mtDNA deletion was even higher than in lymphocytes.

A further shortcoming of the study is that the heteroplasmy rate of the deletion was not determined. Carrying an mtDNA deletion alone does not imply pathology but it is the relation between non-deleted mtDNA (wild-type) and the deleted mtDNA (heteroplasmy) which may be crucial for the pathogenicity of an mtDNA mutation (Zhang, S. *et al.*, 2009). Since the copy number of mtDNA molecules in oocytes has not been systematically investigated (Milani, L., & Ghiselli, F. 2015) and since it is unknown which heteroplasmy rate in oocytes is regarded to be associated with disease, we should be informed about the heteroplasmy rates of the deletion in oocytes from the 52 investigated females.

The study has also the shortcoming that no biochemical, functional, or cybrid studies were carried out to confirm the pathogenicity of the mtDNA deletion and the healthy controls. The deletion can be made responsible for infertility only if the pathogenicity of the variant is confirmed. We should thus be informed if mitochondria in lymphocytes, oocytes, or other tissues showed morphological abnormalities on ultrastructural investigations in those females who carried the mutation.

We also should be informed about the number of probands who finally got pregnant after further IVF trials and how many of these gave birth to a diseased child.

The 4977 bp deletion has been previously reported in association with disease phenotypes such as hepatocellular carcinoma (Guo, Z.S. *et al.*, 2017), peptic ulcer (Salehi, Z. *et al.*, 2017), astheno-zoospermia and oligo-astheno-terato-zoospermia (Ambulkar, P.S. *et al.*, 2016), colorectal cancer (Li, T. *et al.*, 2016), breast cancer (Dimberg, J. *et al.*, 2015), or infertility with varicocele (Gashti, N.G. *et al.*, 2014).

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Thus we should know if any of these features were found in any of the 52 included females or their first degree relatives. In this respect it is also crucial to know if the family history was positive for mitochondrial disease, as 4% of the mtDNA deletions are inherited from the mother's side (Poulton, J. *et al.*, 2017).

Overall, this interesting study could be more meaningful if oocytes would have been investigated, if heteroplasmy rates of the mtDNA deletion would have been determined, if the family history of 52 females with infertility would have been provided, and if the 52 females would have been investigated clinically by a neurologist familiar with mitochondrial disorders for the presence or absence of clinical phenotypic features typical for a mitochondrial disorder.

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