Deep sequencing shows that oocytes are not prone to accumulate mtDNA heteroplasmic mutations during ovarian ageing

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Résumé en anglais	STUDY QUESTION: Does ovarian ageing increase the number of heteroplasmic mitochondrial DNA (mtDNA) point mutations in oocytes? SUMMARY ANSWER: Our results suggest that oocytes are not subject to the accumulation of mtDNA point mutations during ovarian ageing. WHAT IS KNOWN ALREADY: Ageing is associated with the alteration of mtDNA integrity in various tissues. Primary oocytes, present in the ovary since embryonic life, may accumulate mtDNA mutations during the process of ovarian ageing. STUDY DESIGN, SIZE, DURATION: This was an observational study of 53 immature oocyte-cumulus complexes retrieved from 35 women undergoing IVF at the University Hospital of Angers, France, from March 2013 to March 2014. The women were classified in two groups, one including 19 women showing signs of ovarian ageing objectified by a diminished ovarian reserve (DOR), and the other, including 16 women with a normal ovarian reserve (NOR), which served as a control group. PARTICIPANTS/MATERIALS, SETTING, METHODS: mtDNA was extracted from isolated oocytes, and from their corresponding cumulus cells (CCs) considered as a somatic cell compartment. The average mtDNA content of each sample was assessed by using a quantitative real-time PCR technique. Deep sequencing was performed using the Ion Torrent Proton for Next-Generation Sequencing. Signal processing and base calling were done by the embedded pre-processing pipeline and the variants were analyzed using an in-house workflow. The distribution of the different variants between DOR and NOR patients, on one hand, and oocyte and CCs, on the other, was analyzed with the generalized mixed linear model to take into account the cluster of cells belonging to a given mother. MAIN RESULTS AND THE ROLE OF CHANCE: There were no significant differences between the numbers of mtDNA variants between the DOR and the NOR patients, either in the oocytes ($P = 0.867$) or in the surrounding CCs ($P = 0.154$). There were also no differences in terms of variants with potential functional consequences. De-novo mtDNA variants were found in 28% of the oocytes and in 66% of the CCs with the mean number of variants being significantly different (respectively 0.321, $SD = 0.547$ and 1.075, $SD = 1.158$) ($P < 0.0001$). Variants with a potential functional consequence were also overrepresented in CCs compared with oocytes ($P = 0.0019$). LARGE SCALE DATA: N/A. LIMITATIONS, REASONS FOR CAUTION: Limitations may be due to the use of immature oocytes discarded during the assisted reproductive technology procedure, the small size of the sample, and the high-throughput sequencing technology that might not have detected heteroplasmy levels lower than 2%. WIDER IMPLICATIONS OF THE FINDINGS: The alteration of mtDNA integrity in oocytes during ovarian ageing is a recurring question to which our pilot study suggests a reassuring answer. STUDY FUNDING/COMPETING INTEREST(S): This work was supported by the University Hospital of Angers, the University of Angers, France, and the French national research centers, INSERM and the CNRS. There are nocompeting interests.
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