NATURE | NEWS

Non-invasive method devised to sequence DNA of human eggs

The procedure could aid assisted reproduction.

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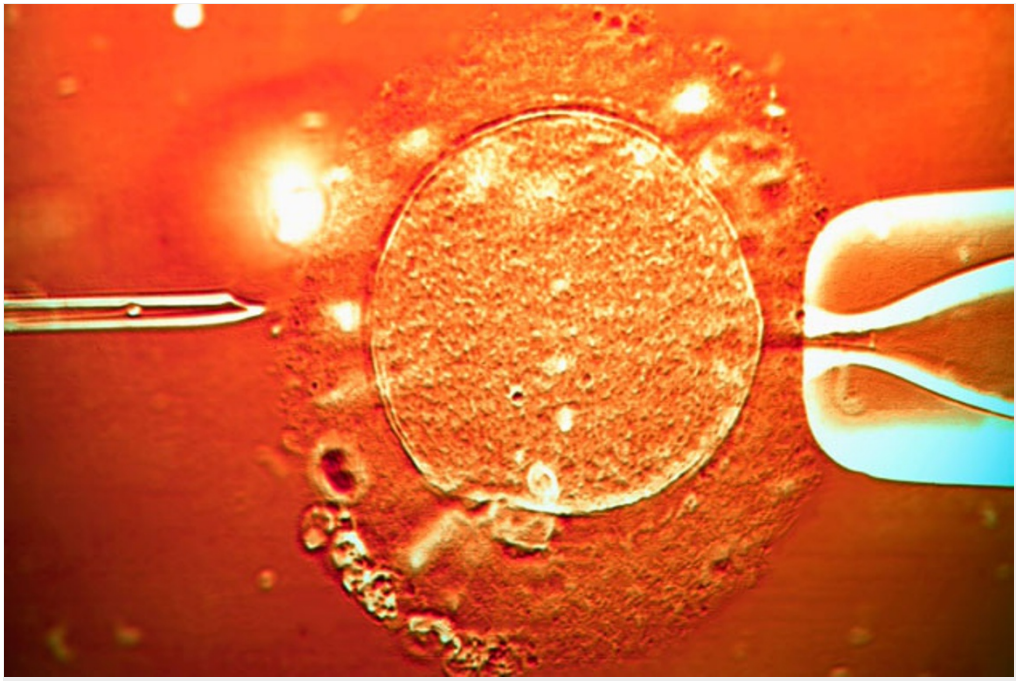
19 December 2013



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Scientists have begun a clinical trial to test whether a new DNA-sequencing technique for human egg cells can improve in vitro fertilization success rates.

Researchers have for the first time determined the genome sequence of human egg cells without destroying them.

The feat, reported today in *Cell*[1], could help couples who undergo *in vitro* fertilization (IVF) by allowing them to choose a genetically healthy embryo to implant into the mother without disturbing the embryo's growth.

“This is a game changer,” says cancer biologist and geneticist Edison Liu, president and chief executive of the Jackson Laboratory in Bar Harbor, Maine.

The work follows the sequencing of individual sperm cells last year[2, 3] by two groups, one led by chemical biologist Sunney Xie at Harvard University in Cambridge, Massachusetts, a co-author of the latest study. Because money from the US National Institutes of Health cannot be used to create or destroy embryos, Xie conducted the latest research with a team at Peking University in Beijing, where he spends one-third of his time.

Egg collection

The team collected eggs from eight mothers, who were paid for their time and discomfort, and fertilized the eggs in a culture dish. They then broke open the resulting embryos and amplified the DNA they contained using a technique called multiple annealing and looping-based amplification cycles (MALBAC).

This last step was important, because there is not enough DNA in a single cell to analyse using a commercial genetic sequencer. But the conventional method of amplifying DNA to gain enough material for analysis — polymerase chain reaction — amplifies some stretches of DNA better than others. Xie’s lab previously developed MALBAC as a way to amplify all portions of the genome evenly, so that more of the cell’s DNA can be read out by a sequencer.

The team then sequenced the female pronucleus, the mother’s genetic contribution to the fertilized embryo that contains one copy of

each human gene. The researchers compared this sequence to that of two other cells that are attached to the embryo but do not become part of the growing baby: the polar bodies, which contain DNA from the mother that is not passed down to her child.

The polar bodies and pronucleus together contain four copies of each of a woman's genes — two from each of her father and her mother. The team showed that it could use the genetic sequence of the polar bodies to accurately predict the genetic sequence of the pronucleus, by counting which three versions of a gene were contained among the polar bodies and thus deducing which version of the gene must be represented in the pronucleus. For instance, if the polar bodies contain two copies of the genes from the woman's father and one from her mother, the pronucleus must contain the second copy of the gene from her mother.

The team showed that it could use this technique to check simultaneously for large chromosomal abnormalities, or aneuplodies, that cause miscarriages, and for disease-causing genes in the mother's DNA. The researchers also sequenced the pronuclei of the egg cells used in the study to prove that the technique correctly predicts their genetic make-up.

Identifying embryos

Bioethicists say that this procedure could be enormously helpful for couples who are trying to identify the best embryos to implant in a mother's womb during the IVF process. This is currently done by removing a cell from a developing blastocyst, an early stage of the embryo, but this raises the fear that the process will disrupt normal development by removing essential material. It also checks for only a sampling of genes, although researchers are beginning to sequence the whole genomes of these cells.

"A non-invasive way to do that analysis would be a fabulous development to improve live birth rates," says Josephine Johnston, a bioethicist at the Hastings Center in Garrison, New York.

IVF specialist Jie Qiao of Peking University, who helped to lead the latest work, has already begun a clinical trial to test whether the method improves IVF success rates. She hopes to enrol 30 women who have genetic diseases or have suffered many miscarriages. Her team will test whether it can help the women to conceive a child by using sequencing to choose the healthiest egg.

Qiao says that the work will not immediately make it possible for couples to create "designer babies" by selecting eggs with desirable qualities. She says that there is still too much uncertainty about how genes influence diseases and traits such as intelligence and appearance, and that conceiving a child through IVF is more difficult, expensive and risky than natural conception. "The long-term safety of this technology remains to be further evaluated," she says.

Philippa Brice, head of communications at the non-profit PHG Foundation in Cambridge, UK, which advocates for the responsible application of medical research, agrees that "it doesn't move things much closer to allowing conception of children with only desired traits, since there is still so much we don't know about which variants influence disease or other traits".

But in the long run, as scientists gain more knowledge about how genes influence traits such as intelligence and appearance, it may become possible to make choices about more aspects of a potential child's genetic make-up.

"IVF is becoming more common," Liu says. He adds that if the genetic selection of eggs and sperm "can be done before fertilization, it is conceivable that over time, the offspring of millions of selective IVFs will alter the genetic landscape of our species".

Recognizing this possibility, Qiao says that society should consider how far the technique can be taken. "More legal regulations need to be built for these types of genomic diagnosis," she says.

Nature | doi:10.1038/nature.2013.14412

References

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