Sperm sequencing could help fight infertility

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Not all sperm are created equal. The first genetic comparison of individual sperm cells has revealed just how diverse they can be. The technology used to study these tiny cells might also be used to study cancer and allow doctors to screen eggs for in vitro fertilisation.

To investigate how much variety there is in one man's sperm, Stephen Quake, Jianbin Wang and their colleagues at Stanford University in California compared sperm cells from a single semen sample.

Analysing the genes of individual cells is notoriously tricky, though. "It's hard to express how difficult single cell experiments are," says Adam Auton at the Albert Einstein College of Medicine in New York. To perform genetic sequencing, you need to amplify, or make lots of copies of the genes within a cell to have enough to analyse. The compounds needed for amplification produce chemical by-products that can make the analysis more difficult.

To overcome this difficulty, Quake's team shrank their experiment onto a microfluidic chip – a device roughly 3 centimetres square and covered in tiny channels and valves. This size of the container meant that a smaller volume of amplification compounds would be necessary, interfering less with the sequencing stage of the experiment.

The group injected a liquid sample containing sperm cells from the ejaculate of one man into the channels of their chip. Valves were set up to separate 91 sperm cells into individual chambers. The team was then able to amplify the genes in each cell in preparation for sequencing.

Do the shuffle

Our genomes contain 23 pairs of chromosomes. When a sperm cell is produced, by a process called meiosis, parts of the chromosomes get shuffled around – a process called recombination. It means that the genetic sequence of each resulting sperm cell varies slightly. It is thought that this process is partly responsible for sibling variation. Recombination also occurs in other body cells, for example, it helps immune cells to rapidly adapt and recognise new pathogens.

Quake's team were able to scan each of the 91 sperm cells' genomes to see if recombination had taken place at any of 1.2 million positions in the DNA. There are certain "recombination hotspots" where recombination often occurs, they say. The team's analysis revealed that chromosomes in some of the sperm cells had recombined in unexpected regions. The findings suggest that the process of genetic reshuffling is unique to each sperm cell. This further adds to the genetic diversity between siblings.

Focus on fertility

The microfluidic chip technique could be used to diagnose recombination problems, which are thought to be one of the causes of male infertility, says Wang. "Previous studies have shown that too much or too little recombination can cause infertility," he says. "This is a way to find

out if recombination is a problem."

Wang hopes that the technique could also help in selecting eggs for in vitro fertilisation (IVF). Each egg cell is produced alongside three other non-functional cells that contain the same genetic code but do not develop into eggs. "We can use those cells to analyse an egg's genome, and screen for genetic diseases," says Wang. Currently, few eggs are screened in this way because existing techniques are so difficult, says Wang. "Our technique may make the process easier."

"It's a great achievement," says Auton, who was not involved in the study. "People have studied single cells before but this is the first time we have been able to look at multiple single cells."

Auton reckons the new technique could also be useful in studying cancer cells. "Every cancer is slightly different," he says. If researchers can study single cells from a tumour, they may be able to get a better idea of which genes have been disrupted by mutations, and develop treatments to target them, he says.

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