New method for diagnosing chromosome errors

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The most common cause of spontaneous abortions is chromosome defects, but they can be difficult to detect. Researchers from the University of Copenhagen have developed a new method that can make

us wiser about how chromosome defects and disease-associated chromosome changes look and how to aid diagnosis.

In Denmark, more and more people are experiencing problems with fertility. The most common cause of spontaneous abortion is chromosome defects. In more than half of the miscarriages that occur during the first 12 weeks, it is because the fetus has a chromosome defect.

Often doctors do not know which chromosome defect is involved. Therefore, it is also difficult to know what the parents can do to complete the pregnancy successfully. However, new research from the University of Copenhagen may help to clarify this.

A newly developed method can characterize chromosomes with an unprecedented level of detail and may help uncover new chromosome errors, which cannot be diagnosed with current methods.

"The dream is that we can take a chromosome sample from a person who has a fertility problem, for example, and then use our method to analyze the chromosomes and determine if something is wrong. It could potentially also be used to investigate other chromosome defects and diseases, for example cancer," says Professor Ian Hickson from the Department of Cellular and Molecular Medicine, who has headed the study.

Today, it is already normal practice at Danish hospitals to examine chromosomes for defects. But the new method will make it possible to examine chromosomes more thoroughly, Ian Hickson explains.

"Today, the chromosomes being examined are exposed to chemicals that fix them. It is like a vet wanting to examine a pet dog, but having to stuff it first," he says.

The chromosomes of a single cell contain two meters of DNA

"We use optical tweezers and a super resolution microscope to examine chromosomes as if they are inside the cells, where they are flexible and mobile. With that method, we can move, press and pull on the chromosomes to see if there are any abnormalities," says Ian Hickson.

With a super resolution microscope, they can see in detail what happens to the chromosome when they manipulate it.

"We can detect more hidden chromosome defects. Maybe the chromosome, for example, falls apart when we pull at one end. Then we know we are dealing with a chromosome defect. But you cannot know that until you have stretched the chromosome," he says.

"With this method we can get a precise calculation of the bare mechanical properties of chromosomes and this can give a detailed view of the underlying structure. If a diseased chromosome has a weaker structure or a weak spot we'll be able to measure it with our method," adds postdoc Christian Friberg Nielsen, one of the main authors of the study.

In order to know what a diseased chromosome looks like, the researchers have first had to investigate several hundred normal chromosomes.

"A chromosome is a remarkable structure. It consists of two DNA molecules. The DNA in the chromosomes of one single cell is two meters long but is packed inside a tiny cell with a diameter smaller than the thickness of a human hair. The two meters of DNA must be packed and folded until chromosomes adopt the characteristic x-shape and only then can we see individual chromosomes using a microscope," says Ian

Hickson.

1% of the world's population lives with a chromosome defect

Ian Hickson emphasizes that there is a very fine balance with chromosomes, and it does not take more than a small chromosome error before it has extensive consequences.

"The most well-known genetic chromosome abnormality is Down Syndrome, which is caused by a child being born with three copies of chromosome 21 instead of two. Whereas a less well known defect, where the embryo has three copies of chromosome 16 is the most common cause of spontaneous miscarriage. It shows how gently balanced the system is," says Ian Hickson.

About 1% of the world's population lives with a chromosome defect. Some can live a normal life, like men with double Y syndrome who have two copies of the male sex chromosome. For others with a chromosome defect it is far more disabling and can result in early death.

The researchers therefore hope that the new method can be used to diagnose chromosomal defects and thus become wiser on how to screen for chromosomal defects in fetuses. In the long term, it might even be possible to help people living with a chromosomal defect, for example by screening their chromosomes in order to suggest treatments that overcome certain features of the defect.

Other forms of chromosomal abnormalities are seen in cancer.

"To put it simply, cancer is a disease of our DNA and chromosomes. It is often obvious when analyzing chromosomes from the affected tissue that a person has cancer and you can see it by the fact that the chromosome

number is very high. For example, 83 or 71 instead of the normal, which is 46. But in many cases it is not as obvious," says Ian Hickson.

In those cases, he hopes the new method can help determine if chromosomes are actually hiding cancer-causing changes.

Ian Hickson estimates that the method probably will be tested in labs for five to ten years before researchers will be able to try it in clinical trials.

"Nonlinear mechanics of human mitotic chromosomes" is published in *Nature*.

More information: Anna E. C. Meijering et al, Nonlinear mechanics of human mitotic chromosomes, *Nature* (2022). DOI: 10.1038/s41586-022-04666-5

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