New chromosome study can lead to personalised counselling of pregnant women

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Foetuses with a so-called new balanced chromosomal aberration have a higher risk of developing brain disorders such as autism and mental retardation than previously anticipated. The risk is 20 per cent for foetuses with these types of aberrations according to a new study from the University of Copenhagen.

These chromosomal aberrations are seen in the foetus in one out of 2,000 pregnant women. Until now, when such an aberration has been found, the medical doctors have told the pregnant woman that the foetus' risk of developing congenital malformations is 6-9 per cent.

"We have identified all the people who, as foetuses, were diagnosed with such a chromosomal aberration in Denmark, and we can see that they more often have developed a disease. The previous study, which found a risk of 6-9 per cent, mainly looked at congenital malformations and did not include neurocognitive diseases such as autism and mental retardation, which often emerge at a later stage. We have therefore been unaware of the extent of the total risk," says one of the authors of the study, Iben Bache, who is associate professor at the Department of Cellular and Molecular Medicine at the Faculty of Health and Medical Sciences and medical doctor at the Department of Clinical Genetics at Rigshospitalet.

Chromosomal Material that Has been Exchanged

"We call these aberrations balanced chromosomal rearrangements, because all the genetic material is still there. There is neither a loss nor a gain of genetic material. The problem is that parts of the genetic material have been exchanged, and that might have caused disruption of an important gene," says Iben Bache.

The study is the largest systematic survey of these rare chromosomal aberrations in foetuses, and it also evaluates the methods that can be used for examining them. These chromosomal abnormalities are diagnosed through chorionic villus sampling or amniocentesis by classical chromosomal analysis, where the genetic material is examined in a microscope. This method has been used for the last 40 years, and it is still the method used in most pregnancies globally.

However, in Danish hospitals the method is increasingly being replaced with another method, chromosomal microarray, which exclusively tests for loss and gain of the genetic material. Chromosomal microarray therefore cannot discover the rare balanced aberrations studied here. In contrast, the study reveals that modern genome sequencing in most cases will be able not only to detect these balanced chromosomal aberrations

but also show whether genes have been damaged. 10.1016/j.ajhg.2018.04.005

The study is a collaboration between researchers at the University of Copenhagen doing basic research, all clinical genetic departments in Denmark and the Department of Epidemiological Research at Statens Serum Institut. The researchers carefully examined the Danish health records to find everyone born with a de novo balanced chromosomal aberration since 1975. Each time they found a person with the aberration, they established a control group of five individuals with normal chromosomes, who had been born more or less at the same time by a mother of the same age.

Provided by University of Copenhagen

The researchers then visited the majority of the persons to do a health examination and collect blood samples for modern genetic analyses. By comparing the health data of the group with the chromosomal aberrations and the control group, the researchers found two-three times higher risk of developing a neurocognitive disorder in the group with the chromosomal aberrations.

In addition, the researchers found that the new whole genome sequencing techniques are much better than any other techniques at assessing the health effect of a balanced chromosomal aberration. This is the conclusion after almost identical assessments made by two independent research groups, including a group from the Harvard Medical School.

"We have not known which analyses to use to discriminate the foetuses that will be healthy from those that will eventually develop disorders. Our study shows that by using the new sequencing technologies we can in fact discriminate in a number of cases. This may greatly affect the diagnosing and counselling of pregnant women carrying foetuses with this specific type of chromosomal aberration in the future," says Iben Bache.

More information: Christina Halgren et al, Risks and Recommendations in Prenatally Detected De Novo Balanced Chromosomal Rearrangements from Assessment of Long-Term Outcomes, *The American Journal of Human Genetics* (2018). DOI: