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Fishing for microdeletions: now researchers can identify sections of DNA that predispose an embryo to develop cancer syndromes in later life

Researchers have used a common laboratory technique for the first time to detect genetic changes in embryos that could predispose the resulting children to develop certain cancer syndromes. Current preimplantation genetic diagnosis techniques can detect mutations in very small bits of genes or DNA, but, until now, it wasn't easy to detect deletions involving whole genes or long sections of DNA in embryos.

The study, published online today (Wednesday 11 March) in Europe's leading reproductive medicine journal *Human Reproduction* [1], uses a technique called fluorescent *in situ* hybridization (FISH) to detect losses of small parts of whole chromosomes (microdeletions) in a single cell from an embryo. The work opens the way to test for microdeletions in patients with other genetic conditions as well as the two cancer predisposition syndromes treated in this study. [2]

Professor Joris Vermeesch, coordinator of the Genomics Core and head of Constitutional Cytogenetics, and Evelyne Vanneste, a PhD student, both at the Center for Human Genetics, University Hospital Leuven (Belgium), and their colleagues used FISH to carry out PGD in embryos from three couples where the women carried microdeletions for either neurofibromatosis type 1 (NF1) or Von Hippel-Lindau disease (VHL). As a result, the woman with the VHL mutation gave birth to healthy twins from embryos selected using FISH PGD.

Neurofibromatosis type 1 (also known as Von Recklinghausen disease) is a common inherited condition with an incidence at birth of one in 3,000-3,500. NF1 patients develop tumours of the nervous system, pigmented patches of skin and can have lower IQs. In 95% of people with NF1, a mutation is found in the NF1 gene, which is a tumour suppressor gene; but five per cent of NF1 patients have microdeletions of the gene, and large microdeletions can result in more severe symptoms.

Von Hippel-Lindau (VHL) disease is a rarer cancer syndrome, occurring in about one in 36,000 births. Symptoms of the disease include benign tumours of the central nervous system and benign and malignant tumours of organs such as the kidneys, adrenal glands and pancreas. It is an inherited condition caused by a mutation in the VHL tumour suppressor gene.

The strands of DNA that twist together to form the double helix structure are made up of lots of small sections called nucleotides. The nucleotides are made up of the four DNA bases – adenine, thymine, guanine and cytosine (or A,T,C,G). Mutations that can be detected by the conventional PCR (polymerase chain reaction) technique used in PGD are usually mutations of a single nucleotide or base. A deletion or microdeletion normally involves the loss of larger numbers of nucleotides.

Prof Vermeesch explained: “Current techniques using PCR to detect abnormalities in embryos can detect one base, nucleotide or letter change in the DNA, but they cannot be used when a person has a loss of the whole gene or a lot of letters – a microdeletion. Patients with these cancer predisposition syndromes, and some other conditions, usually carry only a single microdeletion. Now, for the first time, we have used FISH to detect these microdeletions in the embryo and thus can help carriers to create offspring without those anomalies.

“Importantly, microdeletions are not so rare in neurofibromatosis type 1. It is also becoming clear that genomic disorders caused by microdeletions, duplications and copy number variations are much more frequent than previously thought. The techniques we have used in this study will help a wide range of microdeletion carriers.”

For each of the three women, the researchers created probes that could be used to identify NF1 or VHL deletions in the embryos. The embryos were obtained from the women using normal assisted reproduction techniques. They took two cells from each embryo and performed FISH to probe them for the microdeletions. Only embryos that FISH had identified as being healthy, without any microdeletions, were transferred to the women’s wombs.

Ms Vanneste explained that although they had to make FISH probes specific to each woman, the *NF1* microdeletions found tended to recur. “Therefore, most *NF1* patients with a deletion carry the same deletion and our FISH PGD conditions can be rapidly replicated and re-used in other deletion carriers. It seems likely that the number of families that can benefit from FISH PGD will increase in years to come and we are continuing to help more families using this approach. However, for each condition a new probe has to be made. This is time-consuming, but we are currently developing tools to identify all similar genetic imbalances with a single technology.”

(ends)

[1] Preimplantation genetic diagnosis using fluorescent *in situ* hybridization for cancer predisposition syndromes caused by microdeletions. *Human Reproduction*. doi:10.1093/humrep/dep034

[2] PGD can be carried out already to detect a genetic susceptibility for some cancers, but only if the specific mutation is known (e.g. to detect the BRCA1/2 mutations that can lead to breast cancer developing). The majority of these cases involve a change in a single nucleotide, not a microdeletion.

Notes:

A pdf of the full research paper is available at:

<http://www.oxfordjournals.org/eshre/press-release/freepdf/dep034.pdf>

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