Discovery of new genetic causes of male infertility

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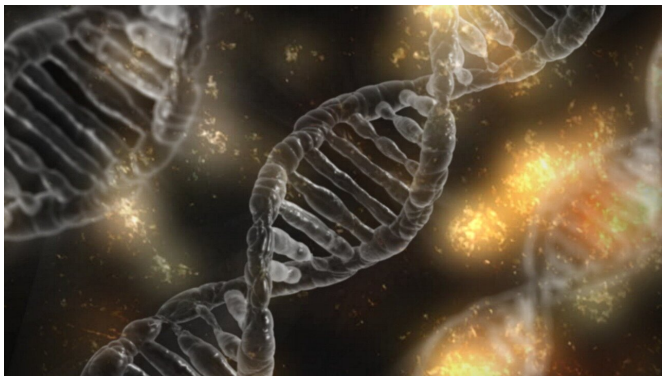

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Infertility—the failure to conceive after a year of unprotected intercourse—affects one in every six couples worldwide, and the man is implicated in about half of these cases. Despite the known importance of genetic factors in the event of the man producing no sperm, only about 25% of these cases can be explained currently. A study to be presented at the annual conference of the European Society of Human Genetics tomorrow (Saturday) has uncovered new potential genetic causes, and this discovery will help to develop better diagnostic tests for male infertility.

Ms Manon Oud, from the Radboud University Medical Centre, Nijmegen, The Netherlands, will describe to the conference how she and her team carried out the first exome sequencing study to investigate the role of de novo mutations (genetic changes that are not present in the DNA of the parents of an individual) in male infertility. The exome is the DNA sequence of genes that are translated into protein, where most of the currently-known disease-causing mutations are situated.

"These de novo mutations are found in every individual and are part of the normal evolution of the genome, "Ms Oud explains. " Mostly they do not affect our health. But in some cases they have a strong effect on gene function and can lead to disease. Until now, their role in male infertility had not been studied."

The researchers studied DNA from 108 infertile men, and also from their parents. Comparison of the parental DNA with that of the offspring enabled the identification of the de novo mutations. " We found 22 in genes involved in spermatogenesis, " says Ms Oud, " none of them previously known to cause infertility in human."

Currently it is too early to give these patients a definitive diagnosis and further studies are ongoing. The researchers hope to screen more patients and their parents in order to search for patterns in the locations of the novel mutations, and to learn more about the function of the genes that are affected by them. "We are studying the role of these genes in material from testis biopsies of our patients and performing experiments in fruit flies to see whether disruption of these genes cause infertility in them, "Ms Oud says.

The results will help establish new diagnostic tests, which will be able to provide a patient with a detailed analysis of the reason for his infertility, and allow for personalised care. By establishing the molecular cause of infertility, the risk of transmitting infertility to another generation can be predicted. "Infertility is not something you normally inherit from your parents; they were clearly both fertile. But with the introduction of assisted reproductive technologies, it is becoming an inherited disorder in some cases, " Ms Oud explains.

The de novo mutations leading to infertility can result from errors in DNA that occur during the production of sperm and egg cells of the parents, or during the early development of the embryo. Although by their very nature these spontaneous mutations cannot be predicted, in other diseases

patients with a highly similar presentation of a disease often have mutations in the same gene. " We therefore expect that there are more infertile men in the world who have mutations in the same group of genes as the group of patients we studied.

"We were surprised to find so many de novo mutations with a potential role in male infertility, given the fact that in previous years only a few novel genes have been discovered in this condition. People still tend to think that failure to conceive is more likely to be caused by a female factor. We are pleased to have been able to make this contribution to the understudied field of male infertility," Ms Oud concludes.

Chair of the ESHG conference, Professor Joris Veltman, Director of the Institute of Genetic Medicine at Newcastle University, Newcastle upon Tyne, UK, said: "The link between genetics and male infertility is something of a mystery, as we pass on our genes but can't pass on infertility. It makes therefore perfect sense to compare the DNA of infertile patients to that of their normally fertile parents, as was done in this study. This new approach may hopefully provide more insight into the underlying causes and help to provide relevant information to couples affected."

More information: Abstract no: C04.4 Exome sequencing reveals de novo mutations and deletions in severe idiopathic male infertility

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