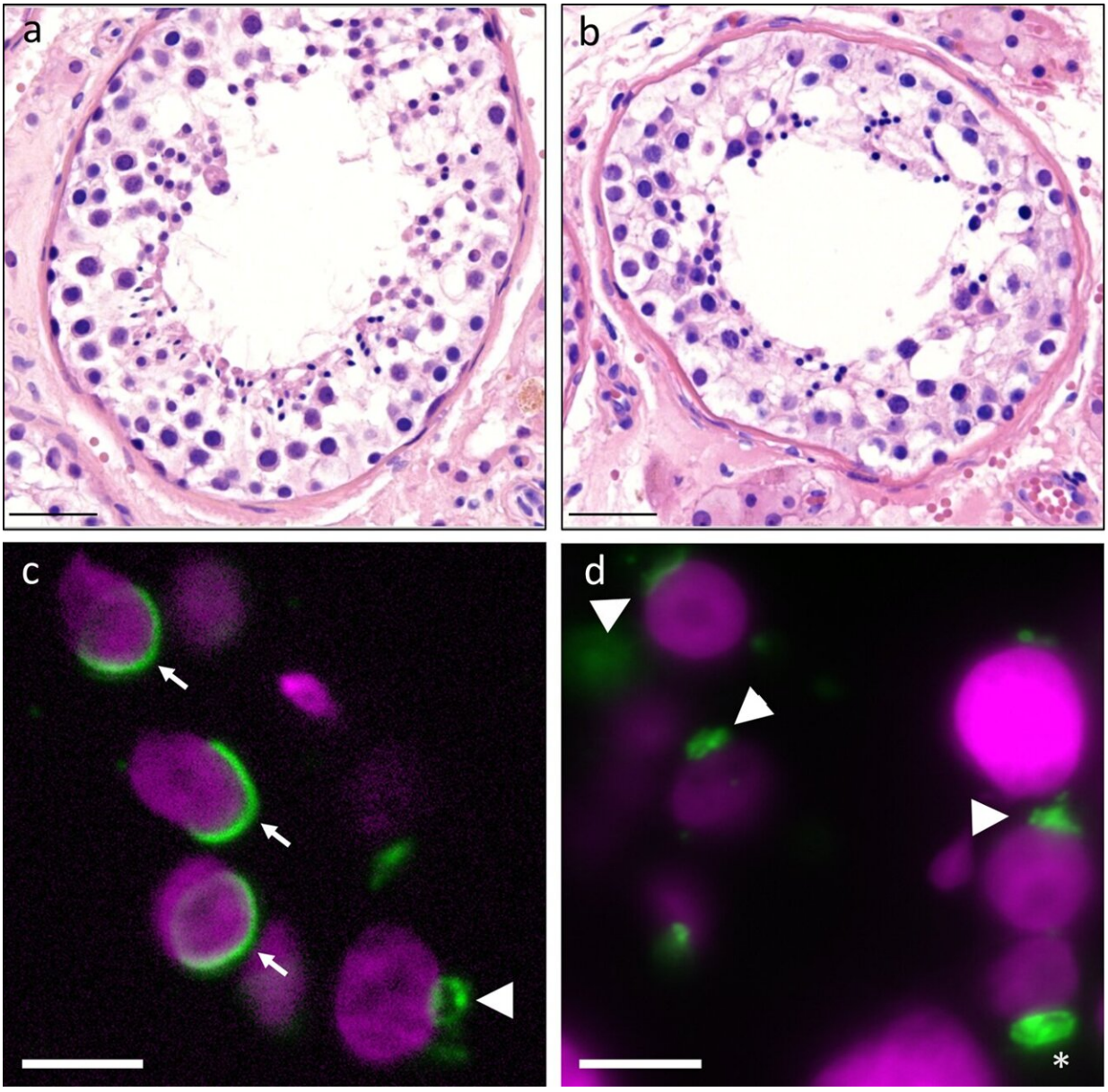
Breakthrough into the cause of male infertility

January 10 2022



Description of control and TOPAZ1 proband testis histology and aberrant acrosome formation. a, b H&E stainings of (a) control and (b) Proband_060 with pathogenic mutations in TOPAZ1 gene. The epithelium of the seminiferous tubules in the TOPAZ1 proband show reduced numbers of germ cells and an absence of elongating spermatids based on the analysis of 150 seminiferous tubules in control and patient. c, d immunofluorescent labeling of DNA (magenta) and the acrosome (green) in control sections (c) and TOPAZ1 proband sections (d). (c) The arrowhead indicates the acrosome in an early round spermatid and the arrows the acrosome in elongating spermatids. Spreading of the acrosome and nuclear elongation are hallmarks of spermatid maturation. (d) No acrosomal spreading (see arrowheads) or nuclear elongation is observed in the TOPAZ1 proband. The asterisk indicates an example of progressive acrosome accumulation without spreading. Scale bar: 40 µm (a, b) and 5 µm (c, d). Credit: DOI: 10.1038/s41467-021-27132-8

Scientists at Newcastle University have identified a new genetic mechanism that can cause severe forms of male infertility.

This breakthrough in understanding the underlying cause of male infertility offers hope of better treatment options for patients in the future.

The study, published today in *Nature Communications*, shows that new mutations, not inherited from father or mother, play a major role in this medical condition.

Experts have found that mutations occurring during the reproduction process, when the DNA of both parents is replicated, can result in infertility in men later in life.

Improving understanding

It is hoped that this new knowledge will help to provide more answers in the future about the cause and best treatment options available to infertile couples.

Professor Joris Veltman, Dean of Newcastle University's Biosciences Institute, led the research which involved patients from Newcastle Fertility Centre and Radboud University Medical Centre in the Netherlands.

He said: "This is a real paradigm shift in our understanding of the causes of male infertility. Most genetic studies look at recessively inherited causes of infertility, whereby both parents are a carrier of a mutation in a gene, and the infertility occurs when the son receives both mutated copies, resulting in problems with their fertility.

"However, our research has found that mutations which occur when the DNA is replicated during reproduction in parents plays a significant role in the infertility in their sons.

"At present, we don't understand the underlying cause in the majority of infertile men, and this research will hopefully increase the percentage of men for whom we can provide answers."

Scientists collected and studied DNA from a global cohort of 185 infertile men and their parents. They identified 145 rare protein-altering mutations that are likely to negatively impact male fertility.

As many as 29 of the mutations affect genes directly involved in processes related to spermatogenesis—the process of sperm cell development—or other cellular processes related to reproduction.

Experts identified mutations in the gene RBM5 in multiple infertile men. Previous research carried out in mice has shown that this gene plays a

role in male infertility.

Importantly, these mutations mostly cause a dominant form of infertility, where only one mutated gene is required. As a consequence, there is a 50 percent chance that infertility caused by these mutations will be passed on to the man's child (if assisted reproductive technologies are used) and this may result in infertility, particularly in sons.

Millions of children have already been born through assisted reproductive approaches as a result of infertility. This research indicates a significant proportion of these children may inherit infertility from their father.

Professor Veltman said: "If we are able to obtain a genetic diagnosis, then we can start understanding better male infertility problems and why some infertile men still produce sperm that can be used successfully for assisted reproduction.

"With our information, and the research others are doing, we hope clinicians can improve counseling for couples and recommend what is the best course of action in order to conceive, either by proposing an appropriate medically-assisted procedure or in cases where none is suitable, provide appropriate alternatives."

Infertility problems

It is estimated that up to 7 percent of men are affected by infertility and 50 percent of fertility problems within a heterosexual couple are due to the man. In around half of male infertility cases, the cause is unexplained.

Moving forwards, the scientists want to expand their work by studying thousands of patients and their parents in a large international

consortium.

They will follow-up their research by conducting further studies into the role these newly identified mutated genes have on the impact of spermatogenesis and on the overall fertility in humans.

More information: M. S. Oud et al, A de novo paradigm for male infertility, *Nature Communications* (2022). DOI: 10.1038/s41467-021-27132-8

Provided by Newcastle University