Genetic link to male infertilty identifed

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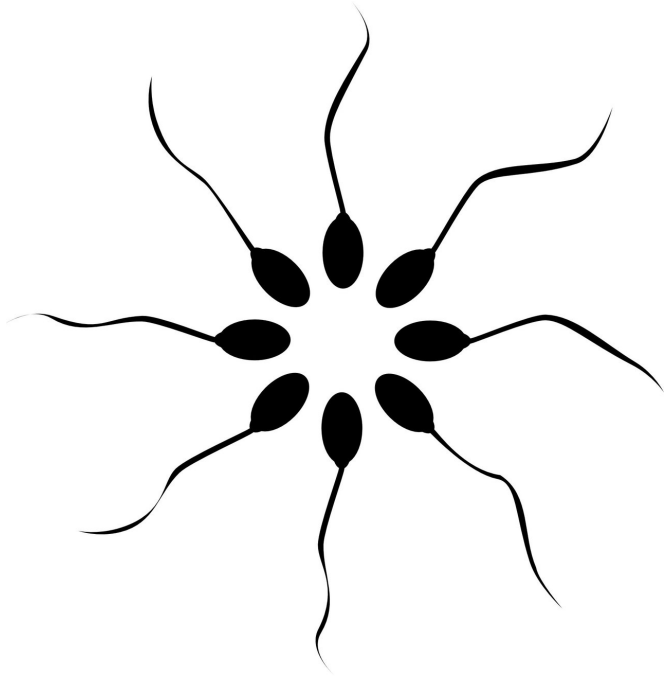

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Researchers have discovered a genetic variant linked to male infertility, which could improve the diagnosis and management of men who carry it. Scientists from the Wellcome Sanger Institute and University of Tartu carried out the largest genetic study to date looking at unexplained infertility in men and found a common subtype of Y chromosome that increases the carrier's risk of fertility issues in a substantial proportion of men of European ancestry.

The findings, published in *eLife*, show that men with this subtype of Y chromosome, have significantly increased risk for genetic mutations affecting the sperm production process (spermatogenesis), and can be almost nine times more likely to have fertility issues. Monitoring for this genetic variant could identify those at higher risk in their early adulthood, giving them a named diagnosis and may allow them to make decisions around future family planning.

Male infertility due to issues with sperm production impacts around 10 percent of men in the UK, but the causes of roughly 60 percent of these cases remain unknown.

In the new study, researchers from the Wellcome Sanger institute and University of Tartu analyzed more than 2,300 individuals from Estonia, with around half of these experiencing unexplained male infertility and half not. They found that some carry a subtype of Y chromosome with an inversion in a genomic region particularly important for spermatogenesis. This inversion itself has no direct effect, but leads to the carrier having a higher chance of genetic deletion of this part of the Y chromosome, which can lead to a low or non-existent sperm count, causing the carrier to be infertile.

However, this Y-chromosome subtype is relativity common and does not always experience genetic deletions or issues with fertility, especially in young men. Therefore, it can be passed on when the carrier has sons, and the carrier may not be identified until they experience fertility issues later in life. This subtype can be found in a significant number of men of European descent but is not found widely in other groups.

Dr. Pille Hallast, co-author and Senior Staff Scientist at the University of Tartu and the Wellcome Sanger Institute, said: "Our study is the largest, most sophisticated look at the genetic variation of this particular Y-chromosomal region that can increase the risk of impaired sperm production in men. By having access to such a large number of patients and reference men, and being able to compare their genetic data to andrological information, we identified a common Y-chromosome subtype that is susceptible to genetic changes leading to low sperm count, but also can go unnoticed and passed down in families until a deletion in this genomic region occurs."

Screening for this subtype, inversion and deletion in a clinical setting when men experience fertility issues will lead to identifying the root cause of the infertility in a proportion of them, which would previously have been labeled unknown. Men who carry the subtype would then be able to make more informed decisions about family planning.

Professor Maris Laan, senior co-author and professor of human genetics at the Institute of Biomedicine and Translational Medicine, University of Tartu, Estonia, said: "Being able to identify the genetic reason for these men having impaired sperm production will help give them a diagnosis and access to the support that this brings. While some deletions on the Y chromosome were previously known to interfere with sperm production, understanding at this level of detail is important for the management of male fertility issues, and in this case the options of having children early in life or preserving sperm for later use could be discussed."

Dr. Chris Tyler-Smith, senior co-author and former senior group leader at the Wellcome Sanger Institute, said: "The biggest surprise is that a Y chromosome subtype with such a deleterious effect on fertility is present in the population at all. Why hasn't it disappeared if it is so harmful? Has it perhaps only started to have this effect on fertility recently, as sperm counts have declined for environmental reasons in the last few decades and resulted in a detrimental combination of genetics and environment?"

10.1093/humrep/dew123

Provided by Wellcome Trust Sanger Institute

More information: Pille Hallast et al. A common 1.6 mb Y-chromosomal inversion predisposes to subsequent deletions and severe spermatogenic failure in humans, *eLife* (2021). DOI: 10.7554/eLife.65420

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