

Genetic factors of male infertility

Background:

The cause of male factor origin infertility associated with oligo-azoospermia is unknown in 50% of cases. These “idiopathic” cases are commonly related to genetic disorders.

One of the most common causes is the presence of a genetic lesion in the azoospermia factor (AZF) region of the Y chromosome. Microdeletion of the AZF region can be detected in about 1 in 10 men with oligo-azoospermia. Microdeletion destroys Y chromosome regions that play an important role in the regulation of spermatogenesis (DAZ, RMBY). Testing is based on the amplification by PCR of known sequences in the AZF A, B and C regions. The failure of amplification is consistent with a microdeletion affecting the tested region. This warrants the involvement of the patient in an in vitro fertilisation programme based on the ICSI technique.

Mutations in the gene for cystic fibrosis (CF) also comprise a relatively common cause of male infertility. Certain mild defects in the CF gene, rather than causing typical cystic fibrosis, result in bilateral obstruction of vas deferens thereby leading to infertility. This may arise from either of two situations – one copy of the CF gene carries a classical, or “severe”, mutation while the other copy contains a “mild” mutation, or both copies carry a “mild” mutation. The best known of the “severe” mutations is the $\Delta F508$, but the R117H, G542X and N1303K mutations are also common. The 5T variant of the IVS8 5T/7T/9T polymorphism is considered a “mild” mutation, which leads to the production of a significantly reduced amount of functional gene product.

Chromosomal factors have a causative role in about 5% of infertile men. This proportion rises to 15% among azoospermic men, with the numerical (63%) or structural abnormalities of the sex chromosomes comprising the majority of cases. Klinefelter syndrome (47,XXY) is the most common sex chromosome aneuploidy, followed by the 47,XYY and 45,X karyotypes and their mosaic forms. Atresia of germ cells leads to azoospermia. Karyotype analysis should be part of the diagnostic workup of every men with oligo- or azoospermia. The molecular genetic test to detect sex chromosome aneuploidy can be used as a faster alternative to the time-consuming cytogenetic analysis, or as a pre-screen.

Indications for testing:

- part of the diagnostic workup of male infertility associated with oligo- and azoospermia
- before the use of assisted reproduction techniques
- other andrological indications

Method:

multiplex PCR and agarose gel electrophoresis (Y chromosome microdeletion), real time fluorescent PCR with hybridisation probes (CF), multiplex fluorescent PCR and capillary electrophoresis (sex chromosome aneuploidy)

Sample requirement:

- buccal swab at room temperature *or*
- 2 ml blood in an EDTA (lavender top) tube, transported at +4 °C

References:

Simoni M, Bakker E, Krausz C.: EAA/EMQN best practice guidelines for molecular diagnosis of y-chromosomal microdeletions. State of the art 2004. Int J Androl. 2004 Aug;27(4):240-9.

Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C.: Male infertility: role of genetic background. Reprod Biomed Online. 2007 Jun;14(6):734-45.