

Y Chromosome Microdeletions

TO DETERMINE THE ETIOLOGY OF AZOOSPERMIA OR OLIGOSPERMIA RESULTING IN MALE INFERTILITY

Disease Overview

- Y chromosome microdeletions are most commonly detected in men with azoospermia (absence of sperm) or severe oligospermia (<1 million sperm/ml semen). Less commonly, men with sperm counts between 1–5 million sperm/ml semen will carry a microdeletion.
- Y chromosome microdeletions frequently involve three azoospermia factor regions (AZFa, AZFb, and AZFc) on the long arm of the Y chromosome that each contain numerous genes involved with spermatogenesis.
- Generalized genotype/phenotype correlations are possible for common microdeletions. Their frequencies have been estimated:
 - AZFa deletion: spermatogenic failure (Sertoli-cell-only syndrome, SCOS) resulting in azoospermia; 5 percent of cases.
 - AZFb deletion: azoospermia/spermatogenic arrest; 10 percent of cases.
 - AZFbc deletion: SCOS/spermatogenic arrest; 13 percent of cases.
 - AZFc deletion: variable phenotype ranging from mild oligospermia to azoospermia and SCOS; 70 percent of cases.
 - AZFabc deletion: SCOS associated with azoospermia; 2 percent of cases.
- Identification of the deleted AZF region has implications for effectiveness of assisted reproductive technologies. Testicular sperm retrieval is ineffective for males with SCOS, which is typically associated with deletions involving AZFa or AZFb, but has been effective for men with AZFc deletions.
- If the male partner has an AZFc microdeletion, intracytoplasmic sperm injection (ICSI) may be an option to achieve pregnancy using in vitro fertilization (IVF). Retrieval of residual sperm may be possible from ejaculate (for men with oligospermia) or from testicular biopsy (for men with azoospermia).
- Y chromosome microdeletions are transmitted to all male offspring if assisted reproductive techniques are utilized. Male offspring are at very high risk for infertility, whereas female offspring are not at increased risk for fertility issues.

Prevalence

- Infertility affects approximately 10 percent of couples of reproductive age. Male-factor infertility is a factor in one-half of these cases.
- Approximately 15–20 percent of infertile men are azoospermic.
- Y chromosome deletions and microdeletions are estimated to occur in one in 2,000–3,000 males.

Genetics

- Inheritance is Y-linked.
- Y chromosome microdeletions typically occur de novo. Rarely, men carrying a microdeletion may be fertile and father infertile sons.
- Penetrance is near 100 percent in affected males.
- Microdeletions of the azoospermia factor (AZF) regions on the q arm of the Y chromosome are present in 5–10 percent of males with non-obstructive azoospermia or severe oligospermia.
- Routine karyotype will detect abnormalities in 5–10 percent of infertile males. Cytogenetic analysis cannot detect Y chromosome deletions, interstitial deletions of the AZF regions, or whether a visible Y chromosome deletion includes the AZF regions.

Indications for Ordering

- To determine the cause of male infertility in men with nonobstructive azoospermia or moderate to severe oligospermia.
- To help predict the effectiveness of assisted reproductive technologies in men with specific Y chromosome microdeletions.

Contraindication

Prenatal testing.

Interpretation

- Lack of detection of an AZF microdeletion greatly reduces the possibility of a Y chromosome deletion being causative for azoospermia or oligospermia.
- Detection of an AZFa, AZFb, AZFbc, or AZFabc microdeletion predicts Sertoli-cell-only syndrome or azoospermia and male infertility. Assisted reproductive technologies are predicted to have decreased efficacy and are not advised.
- Detection of an AZFc may result in a variable phenotype of azoospermia, oligospermia, or abnormal sperm morphology. Assisted reproductive technologies may be effective. All male offspring will inherit the microdeletion.

Methodology

- Multiplex polymerase chain reaction (PCR) followed by gel electrophoresis.
- Analytical sensitivity and specificity are 99 percent.
- Clinical sensitivity is estimated at 5–10 percent for men with nonobstructive azoospermia or severe oligospermia.

Limitations

- Breakpoints of identified microdeletions will not be determined.
- Mutations within individual genes included in the AZF regions will not be detected.
- Rare diagnostic errors may occur due to primer-site mutations.
- Male infertility due to causes other than the common Y chromosome microdeletions tested has not been excluded.

Related Test

[Chromosome Analysis, Peripheral Blood \(0097640\)](#)

References

1. Disteche CM. Y Chromosome Infertility GeneReviews. www.genetests.org (accessed on January 20, 2009).
2. Simoni M, et al. EAA/EMQN best practice guidelines for molecular diagnosis of y-chromosomal microdeletions. State of the art 2004. *Int J Androl* 2004; 27:240–49.
3. Sadeghi-Nejad H and Farrokhi F. Genetics of Azoospermia: current knowledge, clinical implications, and future directions. Part II. *Urol J* 2007; 4:192–206.
4. Practice committee of the American Society for Reproductive Medicine in collaboration with the Society for Male Reproduction and Urology. Evaluation of the azoospermic male. *Fertil Steril* 2008; 90:S74–S77.
5. Ferlin A, et al. Molecular and clinical characterization of Y chromosome microdeletions in infertile men: a 10-year experience in Italy. *J Clin Endocrinol Metab* 2007;92(3):762–70.

Test Information

2001778

Y Chromosome Microdeletions

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.