Y Chromosome Microdeletions

Indications for Ordering

• Determine the cause of infertility in men with
  o Nonobstructive azoospermia
  o Moderate or severe oligospermia
• Help predict effectiveness of assisted reproductive technologies in men with specific Y chromosome microdeletions

Test Description

Multiplex polymerase chain reaction followed by gel electrophoresis

Tests to Consider

Primary test
Y Chromosome Microdeletion 2001778
  • Aid in determining cause of azoospermia or oligospermia
  • Predict effectiveness of assisted reproductive technologies

Related test
Chromosome Analysis, Peripheral Blood 2002289
  • Detect chromosome rearrangements causing oligospermia or azoospermia

Disease Overview

Prevalence
Y chromosome deletions and microdeletions – 1/2,000-3,000 males

Diagnostic issues
• Infertility affects 10% of couples of reproductive age
  o Male-factor infertility is responsible for one-half of cases
• Genetic testing in men with azoospermia or oligospermia when other causes of infertility have been eliminated
  o Chromosomal abnormalities in 5-10% of men
  o Microdeletions detected in 5-13% of men
• Y chromosome microdeletions are most commonly detected in men with
  o Azoospermia (absence of sperm)
  o Severe oligospermia (< 1million sperm/mL semen)
• Y chromosome deletions may be detected in men with sperm counts 1-5 million sperm/mL semen

• Identification of deleted azoospermia factor (AZF) region has implications for assisted reproductive technologies
  o Testicular sperm retrieval is ineffective for males with Sertoli cell-only syndrome (SCOS)
    ▪ Exception is men with AZFc deletion
• Y chromosome microdeletions are transmitted to all male offspring if assisted reproductive techniques are used
  o Male offspring are at high risk for infertility
  o Female offspring have no increased risk for infertility

Genetics

Inheritance – Y linked

Penetrance – near 100%

De novo mutations – most Y chromosome microdeletions are de novo

Mutations
• Microdeletions frequently involve one or more of three AZF regions
  o AZFa – 5% of cases
  o AZFb – 10% of cases
  o AZFc – 70% of cases
  o AZFbc – 13% of cases
  o AZFabc – 2% of cases

Test Interpretation

Sensitivity/specificity
• Clinical sensitivity – ~5-10% for men with nonobstructive azoospermia or severe oligospermia
• Analytical sensitivity/specificity – 99%

Results
• Positive
  o AZFa deletion – spermatogenic failure (SCOS) resulting in azoospermia
  o AZFb deletion – azoospermia/spermatogenetic arrest
  o AZFbc deletion – SCOS/spermatogenic arrest
  o AZFc deletion – variable phenotype ranging from mild oligospermia to azoospermia and SCOS
    ▪ Only AZFc microdeletion appears to be associated with successful assisted reproduction technology
  o AZFabc deletion – SCOS associated with azoospermia
• Negative – lack of detection of AZF microdeletion
  o Greatly reduces the possibility of Y chromosome deletion as the cause of azoospermia or 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 will not be detected