

Genetics of Male Infertility: Role of Androgen Receptor Mutations and Y-Microdeletions

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Abstract

Introduction: Although infertility affects about 5% of the male population, its cause in most cases is uncertain. Normal spermatogenesis depends on a sequential cascade of genetic events triggered by factors encoded by the sex chromosomes. To determine the contribution of genetic aberrations to male infertility, the X-linked androgen receptor gene and the Y-chromosome were examined for mutations in a large cohort of infertile men. **Methods:** Screening of the androgen receptor (AR) gene for single-stranded conformation polymorphisms, confirmation by DNA sequencing, structure-function studies with androgen-responsive reporter genes and chimeric-protein constructs were performed. Y-chromosome microdeletions screening was done with multiplex polymerase chain reaction (PCR) analyses. **Results:** Genetic screening of over 400 patients and controls showed that defects in the androgen receptor gene lead to the production of dysfunctional receptor protein in 15% of males with abnormally low sperm production. The dozens of mutations and polymorphisms uncovered were associated with reduced intrinsic androgen receptor activity and involve principally two regions of the androgen receptor. Gene-transfer experiments implicated defective intermolecular protein-protein interactions with coactivator molecules as the cause of reduced receptor function. Submicroscopic deletions of the Y-chromosome were also been detected in about 6% of patients with severely reduced spermatogenesis. The deleted segments encoded RNA-binding proteins of unknown function and are not linked to defects in the androgen receptor. **Conclusions:** Mutations and polymorphisms of the AR, and Y-microdeletions cause defective sperm production and male infertility in about 20% of subfertile men. These traits can be transmitted to progeny, and counselling can be offered to affected families. Clarification of the molecular mechanisms of pathogenesis has led to rational hormonal therapy.

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