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Molecular Analysis of Y Chromosome Microdeletions in Infertile Men

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ABSTRACT

Idiopathic infertility is a condition of couples unable to conceive for more than two years, with no abnormalities seen on repeated investigations of tubes or as regard with ovulation, luteal phase, cervical mucus, semen, sperm–oocyte interaction or intercourse. Among the major causes of infertility, chromosomal abnormalities, microdeletions, cystic fibrosis transmembrane conductance regulator (CFTR) mutations and other genetic factors (Follicle stimulating hormone (FSH) receptor mutation) are important. Genetic factors cause about 10% of male infertility. Among these, genes in AZF regions including AZFa, AZFb, AZFc and AZFd on the long arm of Y chromosome are considered to be the most important for spermatogenesis. Deletions in these regions are thought to be pathogenetically involved in some cases of male infertility associated with azoospermia or oligozoospermia. The aim of this study was to determine the incidence of AZF deletions among male infertile patients. We analyzed a total of 215 azoospermic infertile men for the presence of 12 sequence tagged site (STS) markers, 3 markers for each AZF region including AZFa, AZFb and AZFc, on the Y chromosome using multiplex PCR. Among the patient group the observed frequency of deletions was about 11.1%, among them the azoospermic men showed more significant deletions (7.4%) than the severe oligospermic men (3.7%) selected for the study. The deletion in AZFa region was 20.83% of the total deletions. The relative frequency of deletions in AZF a, b and c regions in infertile men in this study is AZFa in 1/24 (4.16%); AZFb in 5/24 (20.8%); AZFc in 11/24 (45.83%); AZF a +c in 2/24 (8.3%); AZF b + c in 3/24 (12.5%); AZF a + b + c in 2/24 (8.3%). No microdeletions were found in the control group. According to relatively high incidence of Y chromosome microdeletions among azoospermic patients, molecular screening for detection of these microdeletions seems to be very informative, since different types of these deletions have prognostic value in predicting the outcome of testicular sperm retrieval for assisted reproduction.

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The recent growth of the Indian population has been unprecedented. It is expected to touch 2 billion by 2035 (assuming an average growth rate of 2 per cent). Even though curtailing population is a major National concern, a substantial number of infertile couple in the Indian population have a great concern, that of having a child. This is an equally important national problem concerning the reproductive health for which infertile couple's have to be treated by medically assisted reproductive technology (MART) for procreation (Polani, 2001). Infertility is defined as the state in which a couple wanting a child cannot conceive after twelve months of unprotected intercourse (Mueller and Daling, 1989; Thonneau *et al.*, 1991; American society for reproductive medicine, 2003). It is a problem faced by couples rather than an individual. The male is the sole cause or a contributing cause of infertility in 40 per cent to 50 per cent of infertile couples (Kolettis, 2003).

Causes of infertility can be attributed to male factors such as oligospermia (reduced sperm production) and azoospermia (complete lack of sperm in ejaculate). Men in this infertility category may have an impaired ability to perform basic reproductive functions, such as spermatogenesis (production of healthy sperm). Defective spermatogenesis is the result of a multitude of causes, such as diseases, malnutrition, endocrinological disorders, genetic defects or environmental hazards (Skakkebaek, 1994). Genetic defects such as mutations and chromosomal abnormalities have been estimated to account for atleast 30 per cent of male infertility (Bhasin *et al.*, 1997).

Research in the last 20 years has indicated that the Y chromosome is necessary for sexual development and spermatogenesis. Recent genetic studies of the male infertility have demonstrated the long arm of the Y chromosome (Yq) that harbors atleast 15 gene families (Lahn and Page, 1999), of which some have been shown to be necessary for spermatogenesis. The involvement of the human Y chromosome in male infertility was originally suggested by cytogenetically a detectable terminal deletion of long arm of the chromosome, in which the entire Yq