Journal of Endocrine Disorders

Austin Publishing Group

Open Access Full Text Article

Editorial

Spermatogenic Gene Expression: Fertility and Sterility of Man

Pallav Sengupta[1]*

[1]Department of Physiology, Tribhuvan University, Bhairahawa, Nepal

***Corresponding author:** Pallav Sengupta, Department of Physiology, Tribhuvan University, Universal College of Medical Sciences & Teaching Hospital, Ranigaon, Bhairahawa Siddharthanagar 32900, Nepal, Email: pallav_ucms@yahoo.com ; sunny_pallav_1984@yahoo.co.in

Received: July 24, 2014; **Accepted:** July 25, 2014; **Published:** July 26, 2014

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In experimental models, several genes have been identified for normal reproductive functions, and mutations in these genes cause infertility due to developmental deficiencies of the germ cells. Even with the prevalence of human infertility, few fertility loci have been mapped and about half of all cases of infertility presented by couples can be attributed to the male partners, who are otherwise healthy [1]. The causes of male infertility or subfertility are far ranging, involving chromosomal aneuploidies, translocations, and point mutations for example in the androgen receptors, follicle stimulating hormone (FSH) receptor, and FSH molecule [2]. There is concern in the genes located on the Y chromosome since there are proven correlations between testicular pathology in infertile men and microdeletions associated with specific regions of the Y chromosome [3]. In 1976, karyotyping of azoospermic men revealed deletions on the long arm (Yq) of the Y chromosome4, leading to the azoospermic factor (AZF) hypothesis: the absence of specific fertility genes on the Y chromosome would result in no sperm. Since the microdeletions define these regions, AZFa, AZFb, and AZFc have been named from proximal to distal on Yq. Most (80%) deletions occur in the AZFc region, with 15% and 5%, respectively, occurring in the AZFb and AZFa regions [4]. Deletions occurring across all three AZF regions, although rare, are associated with germ-cell arrest or Sertoli cell–only testes [2]. Within the euchromatic segment of the Y chromosome, the male-specific regions occur on both the short (Yp) and long arms and encode 27 protein-coding genes most of which are mapped to the Yq arm (100). In the AZFa region, the first gene found to be absent in infertile patients was DFFRY (Drosophila fat facets related Y), recently renamed USP9Y (ubiquitin specific protease 9, Y chromosome). This gene is ubiquitously expressed in a variety of tissues and the testis [4]. Deletions of USP9Y have been particularly linked with azoospermia. For the AZFb region, the genes most likely involved in spermatogenesis are those of the RBMY (RNA binding motif on the Y) family. These are expressed only in the germline and their functions are not clear. Most deletions in the Y chromosome that are found in severe oligospermia and azoospermia occur in the AZFc region. The DAZ gene (deleted in azoospermia) is considered responsible for the AZFc phenotype, and it is expressed in primary spermatocytes and spermatogonia.[3] The DAZ gene family consists of four almost identical copies, but different combinations of partial deletions of these gene copies may result in impaired fertility or may have little or no effect on fertility.[4] Partial DAZ deletions are infrequently found in cases of cryptorchidism [4]. Recent studies report that DAZ proteins are also found in fetal gonocytes (the germline stem cells that give rise to the spermatogonia); this and their persistence in spermatids both suggest that DAZ family proteins may act in multiple cell types at multiple points in spermatogenesis. There are possibly thousands of genes encoded on the X and Y chromosomes, as well as the autosomes that influence the process of spermatogenesis [3,4]. Many of these may be expressed not only in the germline but also in the Sertoli cells. Studies of gene inactivations or deletions in knockout mice have shown that more than 200 genes are directly or indirectly involved in male fertility [3,4]. In man, the expression of germ-cell transcripts has suggested that coordinated activities of several thousand genes are linked to full male fertility [1]. Genetic screening of testis cDNA arrays and oligonucleotide array probes of genomic DNA are likely to be developed as diagnostic tools in the future evaluation and selection of treatment options for infertile men. Because testosterone is critical for the maintenance of spermatogenesis, changes to or the absence of a functional AR system will impact androgen signaling and cause moderate-to-severe impairment of germ-cell development [5]. The AR gene is located on the X chromosome and point mutations or excessive CAG (polyglutamine) repeats therein are associated with male infertility [4]. In healthy populations, the number of CAG repeats ranges between 11 and 31; if greater than 40, however, additional disorders arise, including a variety of neurodegenerative diseases [3]. Men with 26 or more CAG repeats in the AR gene have a significantly greater chance of being azoospermic compared with those with fewer repeats, although a recent study[6] reported an absence of larger CAG repeat alleles in 30 azoospermic Japanese men. More data are required to define the normal range of AR gene CAG repeats in order to clarify male infertility risks as well as to determine if intermediate CAG expansions are benign or silent polymorphisms.

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Citation: Sengupta P. Spermatogenic Gene Expression: Fertility and Sterility of Man. J Endocr Disord. 2014;1(1): 1001.

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J Endocr Disord - Volume 1 Issue 1 - 2014
ISSN : 2376-0133 | www.austinpublishinggroup.com

Citation: Sengupta P. Spermatogenic Gene Expression: Fertility and Sterility of Man. J Endocr Disord. 2014;1(1): 1001.