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بالرسالة صفحات

لم ترد بالأصل

HOSSAM MAGHRABY

MOLECULAR GENETIC STUDIES IN SEVERE IDIOPATHIC OLIGO., ASTHENO., TERATO ZOOSPERMIA

Thesis

Submitted to the Faculty of Medicine
University of Tanta
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Doctor in Clinical Pathology

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CONTENTS

LIST OF ABBREVIATION

FSH	Follicle stimulating hormone
LH	Luteinizing hormone
ABP	Androgen binding protein
Gn RH	Gonadotropins releasing hormones
PAR1 and 2	Pseusoautosomal regions 1 &2
NRY	Non recombining region
Yp	Short arm of Y chromosome
Yq	Long arm of Y chromosome
STS's	Sequence tagged sites
TSPY	Testis specific protein, Y
RBMY	RNA binding motif, Y
DAZ	Deleted in azoospermia
CDY	Chromodomain Y
XKRY	XK- related Y
PRY	PTP- bl-related Y; protein tyrosine phosphatase blood related Y
SRY	Sex determining Region Y
DFFRY	Drosophila development fat facets gene
DBY	Dead box polypeptide, Y chromosome
UTY	Ubiquitously transcribed tetracopeptide repeat gene, Y chromosome
USP 9 Y	Ubiquitin specific protease 9 Y chromosome
AZF	Azoospermia factors
SCOS	Sertoli's cell only syndrome
Sxr^b	Deletion interval of the mouse Y chromosome short arm
EIF-1AY	Eukaryotic translation initiation factor 1A, Y isoform
SMCY	Selected mouse c-DNA on the Y chromosome
hn RNP	heterogenous nuclear RNA-binding proteins
BPY122	Basic protein Y1 & 2
TT 4122	Testis transcript Y1 & 2
IHH	Idiopathic hypogonadotrophic hypogonadism
ICSI	Intracytoplasmic sperm injection
FISH	Fluorescene in situ hybridization
PCR	Polymerase chain reaction
FRET probes	Fluorescence resonance energy transfer probes
T	Testosterone
PRL	Prolactin

Introduction

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Fertility means the reproductive potential. It is really a statistical concept with social relevance referring to the reproductive performance as measured in live births *[Potts & Soleman, 1979]*. Normal fertility can be defined as achieving a pregnancy within two years of regular coital exposure. Those couples who do not achieve a pregnancy within two years include the sterile, for whom there is no possibility of a natural pregnancy, and the remainder, who are subfertile. Together, these comprise the infertile. The term sterile may refer to either the male or the female, whereas the term subfertile refers to the couple *[Cates & Rowe, 1987]*.

Infertility is a major health problem affecting 10-15% of couples seeking to have children *[De Kretser & Baker, 1999]*. Biologically it implies that the capacity for producing offspring is diminished; statistically it is observed as a reduction in actual numbers of offspring produced [*Potts & Soleman, 1979*]. A male factor can be identified in about half of these cases, sperm production is defective either qualitatively or quantitatively *[Hargreave, 1994]*.

A significant proportion of infertile males are affected either by oligozoospermia (reduced sperm production) or azoospermia (lack of any sperm in the ejaculate). Such alterations in sperm production may be related in turn to different underlying histological pathologies, ranging from the complete absence of germ cells (Sertoli cell only syndrome) to hypospermatogenesis and maturation arrest *[Cates & Rowe, 1987]*.

The alteration of spermatogenesis can be the consequence of many causes, such as systemic disease, cryptorchidism, endocrinal disorders,

obstruction or absence of seminal pathways, or infections. However, in up to 50% of cases, the results of semen analysis are abnormal but no cause of infertility can be found. Therapeutic approaches are limited because there is inadequate knowledge of the pathogenesis of abnormal spermatogenesis *[De Kretser & Burger, 1997]*.

For a long time, the mammalian Y chromosome was associated with a sole function-sex determination *[Burgoyne, 1998]*. It is well known that it directs the undifferentiated gonad of the early embryo to form a testis. Sex reversal occurs when an individual carries a Y chromosome without a functional SRY gene because of deletion or base substitution. A second role; the control of spermatogenesis was recognized in 1976 when six infertile men were found to have partial deletions of the Y chromosome long arm *[Tiepolo & Zuffardi, 1976]*. With the advance of molecular cloning techniques, new genes have been isolated from the Y chromosome *[Vogt et al., 1997]*.

The involvement of the Y chromosome in spermatogenesis is two fold. Normal spermatogenesis requires not only proper pairing between the X and Y pseudoautosomal regions, but also the products of several genes on Y chromosome long arm. Most of the deletions have been detected by polymerase chain reaction amplification of Y chromosome sequence tagged sites (STSs); a few were determined by Southern hybridization *[Lahn & Page, 1997]*. A majority of the reported deletions fall into three non-overlapping regions on the long arm; indicating the presence of at least three discrete spermatogenesis loci Azoospermia factor regions; AZFa, AZFb, and AZFc. The phenotypes associated with the deletions are variable *[Vogt et al., 1996]*.

Aim of the work

The aim of this will be directed to study the following:

1. The role of Y chromosome microdeletions (Y chromosome long arm) in the peripheral blood lymphocytes in males with severe idiopathic oligo, astheno, teratozoospermia.

2. To correlate between the hormonal and seminal parameters with the Y chromosome microdeletions.

TESTIS

The two major functions of the testis are steroid hormone secretion and spermatogenesis. They are segregated anatomically, with androgen biosynthesis occurring in Leydig cells and spermatogenesis in the seminiferous tubules. The anterior pituitary participates in the control of both of these functions through its secretion of the gonadotropins (Gns), luteinizing hormone (LH) and follicle stimulating hormone (FSH) *[Gharib et al., 1990]*. Thus spermatogenesis is a process that requires complex interactions between different somatic and germ cells within the testis. Thus for spermatogenesis to proceed normally in the seminiferous tubules, Leydig cells and Sertoli cells, the main targets for hormone action in the testis, must receive the physiological signals generated by an intact endocrine testicular axis *[Matsumoto, 1989]*.

Anatomy of testis:

The parenchyma of the testis is composed of large number of convoluted seminiferous tubules, each of which is a continuous loop with its convexity anteriorly, uniting with adjacent tubules posteriorly to open into the rete testis. The tightly coiled seminiferous tubules are arranged in lobules, which constitute about 80% of testicular volume in man. Seminiferous tubules are lined by germ cells and Sertoli cells around a central lumen and surrounded by peritubular myoid cells and basement membrane *[Schulze & Rehdar, 1984]* (Figure I).