



# **Clinical and Cytogenetic Studies of Patients with Sex Chromosome Disorders of Sex Development (DSD)**

*Thesis Submitted for Partial Fulfillment of Master's Degree in  
Pediatrics*

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*To my beloved Mother and Father*  
*All praise to Allah for being blessed*  
*with your kind presence.....*



# دراسات اكلينيكية و وراثية خلوية للمرضي المصابين باختلال الكروموسومات الجنسية لامراض اختلال التكوين الجنسي

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## List of abbreviations:

<b>17OHP</b>	<b>17-hydroxyprogesterone</b>
<b>A</b>	Androstenedione
<b>add</b>	Additional material
<b>AHC</b>	Adrenal hypoplasia congenital
<b>AMH</b>	AntiMullerian hormone
<b>AR</b>	Androgen receptor
<b>AZF</b>	Azoospermia factor
<b>BMI</b>	Body mass index
<b>CAH</b>	Congenital adrenal hyperplasia
<b>CAI</b>	Complete androgen insensitivity
<b>CGY</b>	Cell growth Y
<b>DAX-1</b>	Dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1
<b>DAZ</b>	Deleted in azoospermia
<b>DAZLA</b>	Deleted in azoospermia-like autosomal homolog
<b>DBD</b>	DNA-binding domain
<b>del</b>	Deletion
<b>DHT</b>	Dihydrotestosterone
<b>DHEA</b>	Dihydroepiandrosterone
<b>DHEAS</b>	Dihydroepiandrosterone sulphate
<b>DNA</b>	Deoxyribonucleic acid
<b>DSD</b>	Disorders of sex development
<b>DSS</b>	Dosage sensitive sex reversal
<b>dup</b>	Duplication
<b>DXA</b>	Dual-energy-X-ray-absorptiometry
<b>FGF9</b>	Fibroblast growth factor 9 gene

<b>FISH</b>	Fluorescent insitu hybridization
<b>FMR1</b>	Fragile X mental retardation gene
<b>FOXL2</b>	Forkhead box L2
<b>FSH</b>	Follicle stimulating hormone
<b>FST</b>	Follistatin; activin-binding protein
<b>GBY</b>	Gonadoblastoma Y
<b>GI</b>	Gender identity
<b>GR</b>	Gender role
<b>HCG</b>	Human chorionic gonadotropin
<b>HMG-box</b>	High Mobility Group box
<b>I</b>	Isochromosome
<b>Idic</b>	Isodicentric
<b>INSL3</b>	Insulin-Like factor 3
<b>IQ</b>	Intelligence quotient
<b>LBD</b>	Ligand-binding domain
<b>LH</b>	Luteinizing hormone
<b>LHX9</b>	Lim homeobox gene
<b>Lt.</b>	Left
<b>mar</b>	Marker chromosome
<b>MGD</b>	Mixed gonadal dysgenesis
<b>mos.</b>	Mosaicism
<b>MIF</b>	Mullerian inhibitory factor
<b>NADPH</b>	Reduced nicotinamide adenine dinucleotide phosphate
<b>p</b>	Short arm of chromosome
<b>PAR</b>	Pseudoautosomal regions, termed
<b>PGD2</b>	Prostaglandin D2
<b>PMDS</b>	Persistent Mullerian duct syndrome

<b>POF</b>	Premature ovarian failure
<b>POR</b>	P450 (cytochrome) oxidoreductase
<b>q</b>	Long arm of chromosome
<b>r</b>	Ring chromosome
<b>RPS4X</b>	Ribosomal protein S4, X-linked
<b>RSPO1</b>	R-spondin 1
<b>Rt.</b>	Right
<b>SD</b>	Standard deviation
<b>SF1</b>	Steroidogenic factor 1
<b>SHOX</b>	Short stature homeobox gene on X chromosome
<b>SOX9</b>	SRY (sex determining region Y)-box 9
<b>SRY</b>	Sex-determining region of the Y chromosome
<b>T</b>	Testosterone
<b>TDF</b>	Testes determining factor
<b>TS</b>	Turner syndromes
<b>TSPY</b>	testis specific protein, Y-linked
<b>TSY</b>	Tooth size, Y-linked
<b>U/S</b>	Ultrasound
<b>USP9Y</b>	Ubiquitin specific peptidase 9, Y-linked
<b>WNT4</b>	Wingless-related MMTV integration site 4
<b>WT1</b>	Wilms tumor suppressor gene 1
<b>XIST</b>	X-inactive specific transcript
<b>Yfm1</b>	Y-specific microsatellite marker
<b>ZFX</b>	X-linked zinc finger protein

## **Aim of the work:**

- 1) Studying frequency of sex chromosome disorders among Egyptian DSD patients.
- 2) Phenotype–genotype correspondence of patients with sex chromosome DSD.
- 3) Early detection of Y chromosome material for proper counseling of patients at risk of gonadal tumor development.

## Introduction:

Genetic abnormalities of sexual differentiation are now known as disorders of sex development (DSD) and defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical (**Hughes et al., 2006**).

DSD are not uncommon in Egypt. A previous study has reported an incidence of one newborn with ambiguous genitalia per 3000 live births (**Temtamy et al., 1998**). A more recent study has reported an incidence of 1/5000 with ambiguous genitalia per 20.000 newborns and infants (**Mazen, 2008**).

Disorders of sex development are classified into three main categories: 1) Sex chromosome DSD, 2) 46,XY DSD (including XY gonadal dysgenesis, defects in androgen biosynthesis or action and ovotesticular DSD) and 3) 46,XX DSD (including XX gonadal dysgenesis, ovotesticular DSD and androgen excess) (**Hughes et al., 2006**).

Human sex development is a highly complex process following a cascade of events controlled by multiple genes situated either on the sex chromosomes or autosomes (**MacLaughlin and Donahoe, 2004**).

Y chromosome is strongly male determinant; its short arm contains the SRY gene which is proved to be the testis