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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مقدمه من

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

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

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