بسم الله الرحمن الرحيم


# شبكة المعلومـــــات الجامعية

# التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

# جامعة عين شمس

## التوثيق الالكتروني والميكروفيلم

## ﴿ قـــســـم ﴾

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأفلام قد اعدت دون آية تغيرات

## يجب أن

تحفظ هذه الأفلام بعيداً عن الغبار

في درجة حرارة من 15 – 20 مئوية ورطوبة نسبية من 20-40 %

**To be kept away from dust in dry cool place of**
**15 – 25c and relative humidity 20-40 %**


# بعض الوثائق الأصلية تالفة


# بالرسالة صفحات

# لم ترد بالأصـــل

# DELETIONAL DYSTROPHIN GENE MUTATIONS IN MUSCULAR DYSTROPHY IN EGYPT

*Thesis*
*submitted by*

**Maha Atef Mohamed Tawfik**
M.Sc. (Pediatrics)

*in partial fulfillment of*

**M.D. Degree in Pediatrics**

*FACULTY OF MEDICINE*
*MENOUFIYA UNIVERSITY*
*1995*

# SUPERVISORS


## Prof. Dr. Mohammed Moustafa Hafez,

*Professor of Pediatrics and Genetics,*
*Faculty of Medicine,*
*University of Mansoura.*

## Prof. Dr. Mohammed Ahmed Awadalla,

*Professor of Pediatrics,*
*Faculty of Medicine,*
*University of Ain Shams.*

## Prof. Dr. Soheir Said Abu Elella,

*Professor of Pediatrics,*
*Faculty of Medicine,*
*University of Menoufiya.*

## Dr. Ahmed Abdel Salam Settein,

*Assistant Professor of Pediatrics "Genetics",*
*Faculty of Medicine,*
*University of Mansoura.*

# *ACKNOWLEDGEMENT*

Thanks first and last to ALLAH the most beneficient and merciful. As we owe to him great care, support and guidance in every step in our life.

I would like to express my deepest and sincere gratitude to *Prof. Dr. Mohamed Hafez,* Professor, Head of Pediatric Department, and the Dean of Faculty of Medicine, University of Mansoura, who has offered me much of his valuable time, experience and kind advice throughout the work. His unique organized mind and outstanding scientific abilities helped much to make this work feasible.

I wish to thank with sincere appreciation *Prof. Dr. Mohamed Awadalla,* Professor of Pediatrics, Faculty of Medicine, University of Ain Shams for his genuine and invaluable criticism, being a great scholar, his inspiration and moral encouragement were immeasurable in accomplishing this work.

I am also greatly indebted to *Prof. Dr. Soheir Abou El-Ella,* Professor and Head of Pediatric Department, Faculty of Medicine, University of Menoufiya, for her keen supervision, generous cooperation and kind advice throughout the work.

Special acknowledgement must go to *Dr. Ahmed Settein,* Assistant professor of Pediatrics, Faculty of Medicine, University of Mansoura, who devoted his valuable time, effort and care to help and supervise me going through this work.

My deepest gratitude and thankfulness for *Dr. Ali Shaltout,* lecturer of Pediatrics, Faculty of Medicine, University of Mansoura for his valuable supervision and planning for this work.

My heartiest appreciation and gratitude are due to my husband *Dr. Ahmed Thabet,* Lecturer of Pediatrics, Faculty of Medicine, University of Menoufiya for his scientific and moral support which has been invaluable in this venture. God helps me to be as helpful to him as he is always to me.

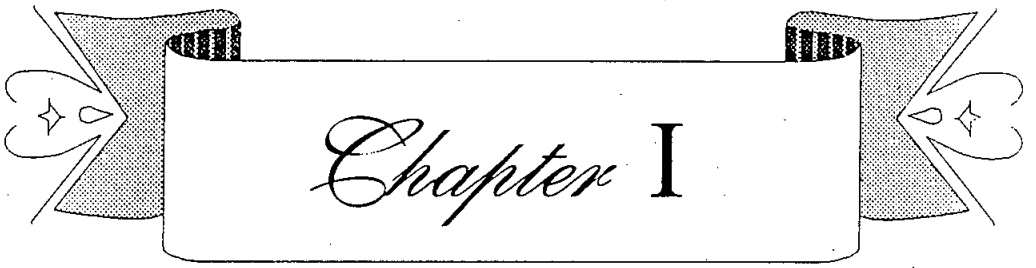
A word of gratitude goes to the *members of Genetic Laboratory Department,* Faculty of Medicine, University of Mansoura for their great help and valuable assistance to finish this work.

Finally, I wish to express my thanks to all patients and their parents for their cooperation which was indispensable for the performance of this work.

# CONTENTS

# Abbreviations

| | |
|---|---|
| DMD | Duchenne muscular dystrophy |
| BMD | Becker muscular dystrophy |
| EMG | Electromyography |
| PCR | Polymerase chain reaction |
| NM | Neuromuscular disease |
| DNA | Deoxyribonucleic acid |
| cDNA | Cloned DNA |
| cM | Centi Morgan |
| Kb | Kilo base |
| bP | base Pair |
| RFLPs | Restriction fragment length polymorphisms |
| mRNA | Messenger Ribonucleic acid |
| mM | millimole |
| I.Q. | Intelligence quotient |
| CPK, CK | Creatine phosphokinase |
| P | Fisher exact test |
| del | Deletion |
| Fam | Family |
| YACs | Yeast Artificial Chromosomes |
| Res | Residence |
| N | Normal |
| Sub | Subnormal |
| LL | Lower limbs |
| UL | Upper limbs |
| Ms | Muscle |
| HFDRs | High frequency deletion regions. |
| EM | Electron microscope |
| CT | Connective tissue |
| PERT | Phenol Enhanced Reassociation Technique. |




# INTRODUCTION AND AIM OF THE WORK

# INTRODUCTION AND AIM OF THE WORK

Duchenne muscular dystrophy is the most common and severe neuromuscular genetic disease in man (Emery et al., 1988). It has an X-linked recessive mode of inheritance, with an incidence of 1/3,500 male births. Duchenne muscular dystrophy is allelic with Becker muscular dystrophy, a clinically similar but less severe form of myopathy affecting 1/30,000 males (Worton et al., 1988). Duchenne muscular dystrophy is characterized by the inability to produce normal dystrophin, a component of membrane cytoskeleton of myofiber (Hoffman et al., 1989).

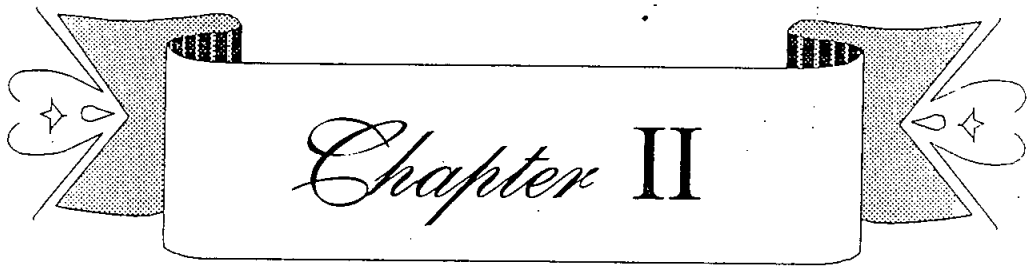
The cloning of Duchenne muscular dystrophy gene led directly to the identification of its protein (Xiuyuan et al., 1990). Because of the large size of the dystrophin gene, the restriction fragment patterns revealed by the cDNA probes are quite complex. So far, the majority of the detectable mutations at this locus are of the deletion type which accounts for about 60% of all mutations (Darras et al., 1988) resulting in the loss of one or more of the 65 exons preferentially clustered in the center of the gene and less frequently near the 5' end (Liechti-Gallatis et al., 1990).

Deletions are not uniformly distributed throughout the gene and deletion rich regions, have been identified. A strong correlation has been observed between the shift in transnational reading frame of a national transcript from such a disrupted gene and the severity of patient's disease, while the size and position of the disruption appear less important (Monaco et al., 1988).

Duplication of part of the Duchenne muscular dystrophy gene has also been revealed in a few patients (Xiuyuan et al., 1990).

Rapid detection of deletion and duplication mutations that cause Duchenne and Becker muscular dystrophy was achieved in patients and carriers after amplification of small amounts of mRNA from peripheral blood lymphocytes (Roberts et al., 1990). Such deletions are readily identified in patients by the absence of bands from Southern blots (Speer et al., 1989) or by failure of amplification of individual reactions in multiplex polymerase chain reaction (Saiki et al., 1988, Chamberlain et al., 1988). However diagnosis is complicated in carrier women by the presence of the normal chromosome which masks the results from the defective chromosome (Roberts et al., 1990).

The aim of this work is detection of the different types of deletions in the dystrophin gene that may lead to the Duchenne or Becker muscular dystrophy in affected Egyptian patients, this will greatly facilitate the arrangement for a programme of prevention through detection of carriers and prenatal diagnosis in the proband's families.




# REVIEW OF LITERATUTRE