سامية محمد مصطفى

شبكة المعلومات الجامعية

بسم الله الرحمن الرحيم

سامية محمد مصطفى

شبكة المعلومات الجامعية

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

سامية محمد مصطفى

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

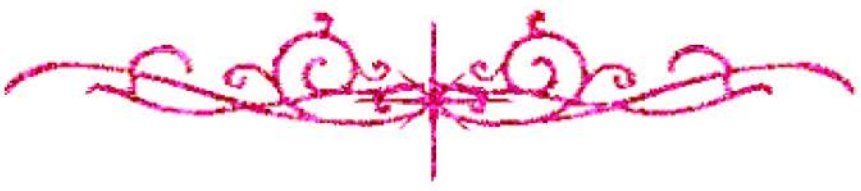
يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

سامية محمد مصطفى

شبكة المعلومات الجامعية

بعض الوثائق الأصلية تالفة



سامية محمد مصطفى

شبكة المعلومات الجامعية

بالرسالة صفحات لم ترد بالأصل

Intercellular Adhesion Molecule sICAM-1 in Children with β-thalassemia Major

THESIS

Submitted to The Faculty of Medicine
Alexandria University
in partial fulfillment of the requirements
for
Master Degree
of
(Paediatrics)

By

Gihan Nabil Ahmed Mahmoud

M.B.B.Ch., Alex.

Medical Research Institute
Alexandria University
2000

SUPERVISORS

Prof. Dr. Bothaina Abd El Fatah El Domiaty

Professor of Paediatrics

Faculty of Medicine

Alexandria University

Prof. Dr. laila El Sayed Ziada

Professor and Head of Department of Haematology

Medical Research Institute

Alexandria University

Dr. Ragia Hussein Badawy

Lecturer of Haematology

Medical Research Institute

Alexandria University

Co-worker

Dr. Hoda Mohamed Aboul Fetouh Hassab

Assistant Professor of Paediatrics

Faculty of Medicine

Alexandria University

Acknowledgement

Praise **GOD** for his help, without it this work would have been impossible.

I would like to express my deepest gratitude to **Prof. Dr. Bothaina A. El Domiaty**, Professor of Paediatrics, University of Alexandria. She directed me during the work and was a great help during the final stages of production of this thesis.

I am deeply thankful to **Prof. Dr. Laila E. Ziada**, Professor and Head of Department of Haematology, Medical Research Institute, University of Alexandria, for her continous encouragement, sincere advice and kind supervision throughout this work.

My deepest appreciation is due to **Dr. Ragia H. Badaway**, Lecturer of Haematology, Medical Research Institute, University of Alexandria, who was a great help, step by step during the work.

Last but not least is the part participated by **Prof. Dr. Hoda M. Hassab**, Assistant Professor of Paediatrics, University of Alexandria. I like to thank her cordially for her great help and meticulous revision of the text.

CONTENTS

LIST OF ABBREVIATIONS

Hb	:	Haemoglobin
DFO	:	Desferrioxamine
BMT	:	Bone marrow transplantation
IL	:	Interleukin
IFN	:	Interferon
TNF	:	Tumor necrosis factor
LFA	:	Lymphocyte function antigen
NK	:	Natural killer cells
HIV	:	Human immunodeficiency virus

INTRODUCTION

INTRODUCTION

β-Thalassemia Major

The name thalassemia is derived by contraction of thalassic anhaimia from the Greek thalassa-sea, an-none and haimia-blood.[1] The thalassemias are a diverse group of autosomal recessive inherited congenital disorders in which there is a defect in the synthesis of one or more of the subunits of haemoglobin.[2] This haemoglobinopathy is caused by several genetic mutations[3], the mild forms of which are among the most frequent genetic defects in humans.[4] β-thalassemia results from point mutations within or close to the β-globin gene complex resulting in reduction or abolition of β-globin gene function and so to β^+ or β^0 thalassemia.[1]

β-Globin Gene

Normal individuals carry two β-globin gene clusters, one on the short arm of each chromosome 11.[1]

The β-gene cluster includes five functional genes.[4,5]

ε gene: Encodes for the embryonic haemoglobins Hb Gower 1 and 2.

γ gene: Encodes for γ-globin found in haemoglobin F and are duplicated.

α gene: Encodes for α globin.

β gene: Only a single functional β-globin gene is found in the cluster.

Molecular Pathology

Genetic defects affecting β-globin gene in β-thalassemia are either deletions or mutations.[1]

1- Gene deletions

Several deletions causing β-thalassemia have been described[6] but all except one are extremely rare.[5] The most prevalent is a deletion that begins in the second intervening sequence and extends beyond the 3′ end of the β-globin gene[7], and it is associated with typical high HbA_2 β^o-thalassemia.[4]

2- Mutations

So far about 150 point mutations have been described that give rise to β-thalassemia. There are phenotypic differences between many of these mutations.[8] These mutations are classified according to the stage of globin gene expression at which the defect is manifest into those that alter β-globin mRNA transcription and those that affect mRNA processing.[1]

I- Mutations affecting mRNA transcription

(a) Promotor region mutations

These mutations reduce binding of RNA polymerase, thereby reducing the rate of mRNA transcription to 20 to 30% of normal.[7] The β-globin synthesis, even in homozygous, is sufficient to

preclude thalassemia major.[9] Some of these defects are even so mild to be only associated with "silent carrier" phenotype in heterozygous.[10]

(b) Chain terminator mutations.

i) Non-sense mutations

A single nucleotide substitution alters a codon that is normally decoded into an amino acid to one that stops translation.[7]

ii) Frame shift mutations

A nucleotide deletion or insertion changes the grouping of nucleotide triplets or codons, thereby garbling the gene's message down stream from the mutation. Such shift creates terminator codons from base sequences that are normally in adjacent codons.[11]

The mRNA produced by the chain terminator mutations is incapable of being translated into full-length globin chains resulting in the β^{o}-thalassemia.[12]

II- Mutations affecting mRNA processing

(a) Splice junction mutations

Point mutations involving the donor or acceptor dinucleotides at either end of the intervening sequences result in abnormal splicing. The altered mature RNA resulting from these mutations is useless as a messenger for β-globin synthesis.[1]

(b) Mutation creating new splice signals

Several nucleotide substitutions within introns involve sequences that differ only slightly from normal splice sites. These mutations have the effect of changing a cryptic splice site to a legitimate one. The new splice sequences and the new site is used preferentially by the normal donor site. These mutations cause premature termination of mRNA.[13]

(c) Enhanced cryptic splice site

A silent mutation involves codon 24. It does not give rise to a variant haemoglobin nor to increased HbA_2. It results in a mild thalassemia phenotype.[4]

(d) RNA cleavage defect

Normally, the six nucleotides at the end of the third exon trigger an enzymatic process that cuts the growing mRNA at the appropriate point. Base substitutions change this signal allowing transcription to continue to the next cleavage signal, thus doubling the length of pre-mRNA and renders it unstable.[7]

(e) Cap site mutation

A cap site variant has been described in association with the β^+ thalassemia phenotype. Substitution of cytosine for arginine in the first position may reduce transcription or slow the 5′ capping process, thereby reducing mRNA stability.[7]