Growth Differentiation Factor ١٥ in Beta Thalassemia

Thesis

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List of Abbreviations

٣'UTR : ٣' untranslated region

ALT : Alanine transaminase

AST : Aspartate transaminase

ATO : Arsenic trioxide

BM : Bone marrow

BMI : Body mass index

BMPRs : Bone morphogenic protein receptors

BMPs : Bone morphogenic proteins

C/EBPα : CCAAT/enhancer-binding protein

CE- HPLC : cation exchange high performance liquid chromatography

CHO : Carbohydrate

CHOP : CCAAT/enhancer-binding homologous protein (negative regulator of C/EBPα)

CREBH : cAMP-responsive element binding protein H

DFO : Desferoaxamine

DFP : Deferiprone

DNA : Deoxyribonucleic acids

EDTA : Ethylene diamine tetra-acetic acid

EMH : Extramedullary hematopoiesis

EPO : Erythropoietin

EPOR : EPO receptor

ESR : Erythrocyte sedimentation rate

GDF١٥ : Growth differentiation factor ١٥

Hb : Hemoglobin

HFE : HFE gene product

List of Abbreviations

HJV : Haemojuvelin
HPFH : Hereditary persistence of fetal hemoglobin
HPLC : High-performance Liquid chromatography
HS : Hypersensitive sites
HSM : Hepatosplenomegaly
IL-١ : interleukin -١
IL٦R : IL-٦ receptor
IQR : Interquartile range
IVS : Intervening sequence
LAR : Locus activating region
LCR : Locus control region
MCH : Mean corpuscular hemoglobin
MCHC : Mean corpuscular hemoglobin concentration
MCV : Mean corpuscular volume
MDD : Minimum detectable dose
MIC-١ : Macrophage inhibitory cytokine – ١
MMP : Mitochondrial membrane potential
Mr : Monomer molecular mass
mRNA : Messenger ribonucleic acid
NAG-١ : Nonsteroidal anti-inflammatory drug activated gene
PB : Peripheral blood
PCR : Polymerase chain reaction
PDF : Prostate derived factor
PLAB : Placental bone morphogenic protein
PLT : Platelets

List of Abbreviations

PTGFb : Placental transforming growth factor-b

RDW : Red cell distribution width

ROC : Receiver operator curve

SCF : Stem cell factor

sHJV : Soluble form of Haemojuevelin

Smad : Small molecules against decapentaplegic proteins

STAT : signal transducer and activator of transcription

TF : Transcription factor

Tf : Transferrin

TGF-β : Transforming growth factor-β

TIBC : Total iron binding capacity

TLC : Total leucocytic count

TM : Thalassemia major

TNFα : tumour necrosis factor α

TT : Thalassemia trait

TWSG١ : Twisted gastrulation

Tx : Thromboxne

UPR : Unfolded protein response

XBP-١ : X-box binding protein ١ (endoplasmic reticulum stress-activated transcription factor)

γGT : Gamma glutamyl transferase

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Introduction

The thalassemia syndromes (alpha and beta thalassemia) represent the most common causes of ineffective erythropoiesis ***(Tanno et al.,).*** The increased but ineffective erythropoiesis resulting in tissue iron overload ***(Casanovas et al.,)*** induces numerous endocrine diseases, hepatic cirrhosis, cardiac failure and even death ***(Weatherall and Clegg,).***

Hepcidin regulated intestinal absorption represents a principal mechanism for iron homeostasis in humans ***(Donovan et al., ٢٠٠٦).*** It is commonly believed that ineffective erythropoiesis inhibits expression of hepcidin, a hepatic peptide hormone secreted from liver that regulates the release of iron into the blood stream from duodenal enterocytes, hepatocytes and macrophages ***(Ramey et al.,).*** It was shown that hepcidin levels are decreased in individuals with beta thalassemia syndromes ***(Kattamis et al., ٢٠٠٦).***

It's hypothesized that the erythroid expansion could influence the regulation of hepcidin expression through systemic release of transforming growth factor β (TGF-β) superfamily members that are secreted from erythroblasts during human erythropoiesis ***(Tanno et al., ٢٠٠٧).***

The TGF-β superfamily consists of numerous molecules that regulate cellular processes such as growth differentiation and oncogenesis. Members of the TGF-β superfamily include

several TGF-β proteins, bone morphogenetic proteins (BMPs), growth differentiation factors (GDFs) and other proteins ***(De Caestecher and M,*** ***).***

Growth differentiation factor ١٥ (GDF١٥),a member of the transforming growth factor β superfamily acts by inhibiting hepcidin expression, therby contributing to iron overload in thalassemia syndromes ***(Tanno et al.,*** ***٢٠٠٧).***

GDF١٥ measurements may be helpful for predicting ineffective or apoptotic erythropoiesis ***(Tanno et al.,*** ***);*** further evaluation of its levels in thalassemia patients may have useful clinical applications.

Aim of the Work

In this study we aim to analyze GDF١٥ levels in β-thalassemia patients in conjunction with their iron status and clinical presentation.

Thalassemia

The thalassemias are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more of the globin chains of hemoglobin. The result is imbalanced globin chain production, ineffective erythropoiesis, hemolysis and variable degrees of anemia ***(Weatherall, ٢٠٠٦)***.

Geographic distribution and epidemiology

Thalassemia is the most common genetic disorder all over the world. Around ٣٪ of the world population carries genes for β-thalassemia ***(Omar et al., ~).***

β-thalassemia is distributed widely in Mediterranean populations, Middle East, parts of India and Pakistan, and throughout Southeast Asia. The disease is common in parts of the southern Soviet republics and in the People's Republic of China. β-thalassemia is rare in Africa, except for isolated pockets in West Africa, notably Liberia, and in parts of North Africa ***(Weatherall and Clegg, a)***.

In Egypt β-thalassaemia is the most common genetically determined, chronic haemolytic anaemia with an estimated carrier rate of ٩٪–١٠,٥٪ ***(Madani et al.,)*** and a gene frequency of ٠,٠٣. So, it was estimated that ١٠٠٠/١,٥ million per year live births suffer from thalassemia disease in Egypt ***(Ahmed et al.,)***.

The most common forms of thalassemia are those that are prevalent in the malarial tropical and sub-tropical regions where a few mutations have reached high gene frequencies because of the protection they provide against malaria.The epidemiology of the disease; however is changing due to a fall in total birth rate, prevention programs and recent population movements ***(Swee,)***.

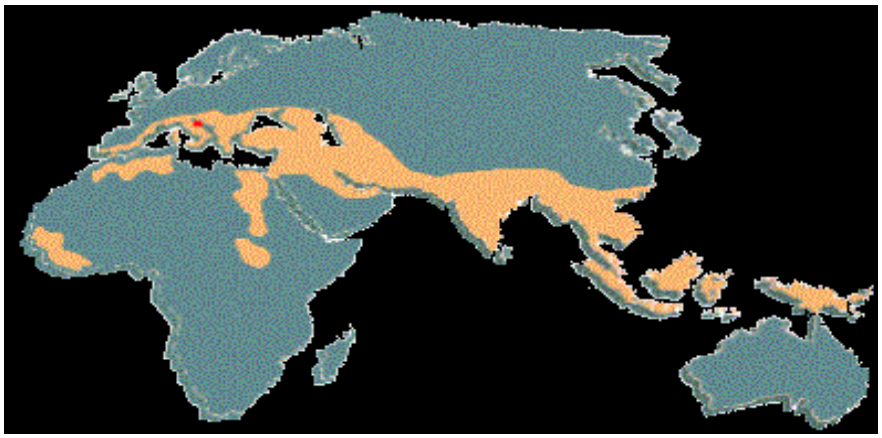

Figure (١): Geographic distribution of β-thalassemia ***(Weatherall and Clegg, b).***

Classification of Thalassemias

They are divided into two main classes, α and β according to which globin chain is produced in reduced amounts ***(Cornelis and Douglas,).***

β-Thalassemias:

β-thalassemias, which are caused by a decrease in the production of β-globin chains, are the most important types ***(Cunningham et al.,).*** β-thalassemia is divided into two main varieties: