EFFECT OF VITAMIN D RECEPTOR GENE POLYMORPHISMS ON GROWTH AND BONE MINERAL DENISTY IN HOMOZYGOUS BETA-THALASSEMIA

Thesis

SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE IN PEDIATRICS

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2005

And say, 'My Lord!
Increase My Knowledge'

Acknowledgement

Thanks to **God** first and foremost. I feel always indebted to **God**, the most kind and the most merciful.

I would like to express my gratefulness and respect to ***Prof. Azza Abdel Gawad Tantawy,*** Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her endless support and guidance. She encouraged me and pushed me forward to achieve success.

I wish to express my deep thanks and appreciation to ***Prof. Heba Hassan El Sedfy***, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her great support, extremely valuable help and major contribution to the completion of this thesis.

I would like to express my gratefulness and respect to ***Dr. Tarek Mustafa*** assistant Prof. of Pediatrics, Genetic Department, Faculty of Medicine, Ain Shams University for his great support and continuous guidance.

Also I would like to express my greatfulness and appreciation to ***Dr. Mona Rashad*** lecturer of

Pediatrics,Faculty of Medicine- AIN Shams University for her great support.

In addition, much deserved thanks go to everyone who assisted me in achieving this thesis.

I would like to acknowledge a special debt of gratitude to my family for their great support, encouragement which was greatly helpful for me to overcome all obstacles in my way and to complete this work.

Contents

List of Abbreviations

25(OH) D	25- hydroxyvitamin D
Bp	Base pair
BM	Bone marrow
BMT	Bone marrow transplantation
BMD	Bone mineral density
DBD	DNA-binding domain
DBP	Vitamin D- binding protein
DFO	Deferoxamine
ERG	Estrogen receptor gene
FBMD	Femoral bone mineral density
GIT	Gastrointestinal tract
Hb F	Hemoglobin F
LBD	ligand-binding domain
LBMD	Lumbar spine bone mineral density
MHC	Major histocompatibility complex
NHRS	Nuclear hormone receptors
PCR	Polymerase chain reaction
PTH	Parathyroid hormone
RBCS	Red blood cells
RFLP	Restriction fragment length polymorphism
RXR	Retinoid X receptor
VDR	Vitamin D receptor
VDREs	Vitamin D response elements

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INTRODUCTION

Bone disease frequently occurs during the clinical course of homozygous β thalassemia despite regular transfusions and iron chelation therapy *(Ferrara et al., 2002).*

The high prevalence of short stature and low or very low bone mass in optimally treated β thalassemia patients has been associated with several factors such as chronic anaemia,endocrine disorders,life style,iron overload and with high doses of desferrioxamine unrelated to tissue iron burden *(Jensen et al., 1998).*

Moreover, the inheritance of bone density and growth is under polygenic control such as COLIA 1 and COLIA 2 genes, vitamin D receptor (VDR) gene and oestrogen receptor gene *(Perrotta et al., 2000).*

It has been observed that there is a relationship between growth and Fok1 or Bsm1 vitamin D receptor polymorphisms in a healthy population *(Minamitani et al., 1998; Tao et al., 1998).*

Aim of the work

The aim of this study is to perdict bone density from the common allelic variations in the vitamin D receptor gene locus.

Thalassemia

Definition

The thalassemia syndromes are a heterogeneous group of inherited anemias characterized by defects in the synthesis of one or more globin chain subunits of the adult hemoglobin tetramer (HbA). This leads to deficient hemoglobin accumulation, resulting in hypochromic and microcytic red cells and ineffective erythropoiesis and hemolytic anemia. It is inherited as an autosomal recessive disorder *(Honig, 2000).*

Hemoglobin is the substance in red blood cells that enables them to transport oxygen throughout the body. It is composed of a heme molecule and protein molecules called globins. Normal hemoglobin molecules contain two pairs of different globin molecules. Humans have the genes to construct six types of globins, but do not use all six at once. Different globins are produced depending on the stage of development: embryonic, fetal, or adult. During embryonic development, hemoglobin contains two zeta-globin molecules and two epsilon-globin molecules. At the fetal stage, the body switches to alpha-globin and gamma-globin production. Within weeks after birth, an infant continues to produce alpha-globin, but gamma-globin is replaced by beta-globin and a very minor amount of delta-globin. After the first two to three months of life, most hemoglobin in the body is

composed of two alpha-globins and two beta-globins; approximately 0.5% is composed of two alpha-globins and two delta-globins. Thalassemia is classified according to the globin that is affected. The most common types of thalassemia are beta-thalassemia and alpha-thalassemia (*Weatherall, 1995*). Hemoglobin properly binds and releases oxygen only when two alpha subunits are connected to two beta subunits. A pair of genes located on chromosome 16 controls the production of the alpha subunits of hemoglobin. A single gene located on chromosome 11 controls the production of the hemoglobin beta subunit (*Giardini et al., 1997)*.

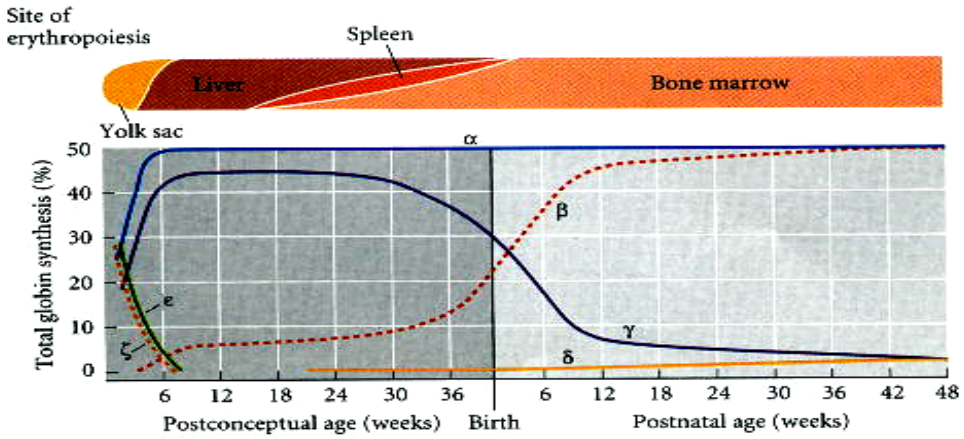

Fig (1): Percentages of hemoglobin chain types as a function of human developmental stage (*Karlsson et al., 1998*).

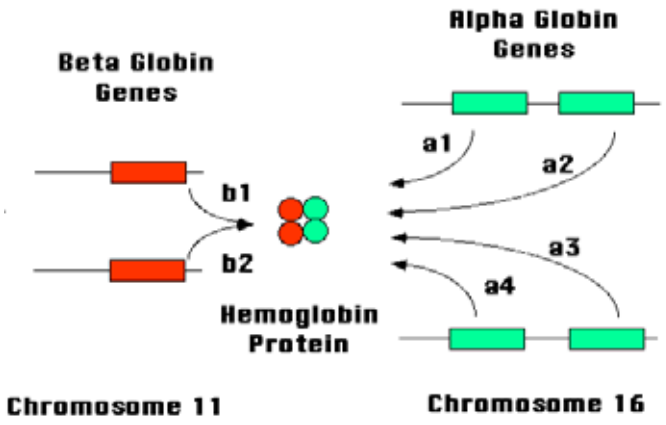

Fig (2): The two chromosomes 11 have one beta globin gene each (for a total of two genes). The two chromosomes 16 have two alpha globin genes each (for a total of four genes). Hemoglobin protein has two alpha subunits and two beta subunits. Each alpha globin gene produces only about half the quantity of protein of a single beta globin gene. This keeps the production of protein subunits equal. Thalassemia occurs when a globin gene fails, and the production of globin protein subunits is thrown out of balance (***Karimi, 2003).***

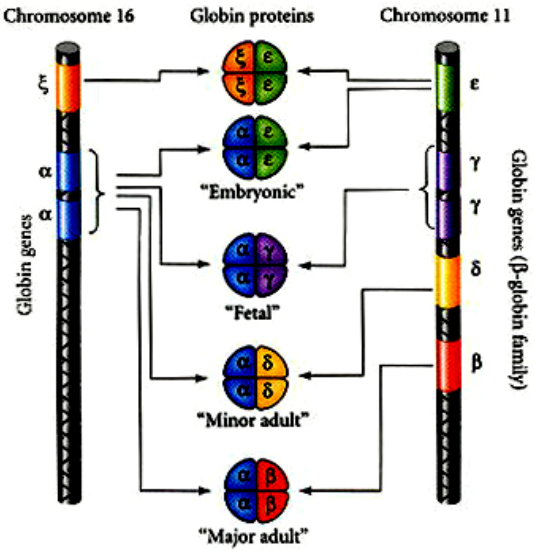

Fig (3): Diagram of the human β-globin family of genes on chromosome 11. Downstream from the Σ-globin (embryonic) gene are two nearly identical γ-globin (fetal) genes. These are followed by the adult δ-and β-globin genes (***Weatherall, 2000).***

Alpha thalassemia

Occurs when one or more of the four genes needed for making the alpha goblin chain of hemoglobin are variant or missing. Moderate to severe anemia results when more than two genes are affected. Alpha thalassemia major can result in miscarriages. It is commonly found in people from Africa, the Middle East, India, Southeast Asia, southern China, and sometimes from the Mediterranean.

There are several different types of alpha thalassemia, ranging from mild to severe:

- Silent carrier state – (only one gene affected) - only a small lack of alpha protein, so generally there are no health problems.
- Alpha thalassemia trait or mild alpha thalassemia – (with two genes affected) lacking enough alpha protein to sometimes cause mild symptoms which are similar to iron deficiency anemia.
- Hemoglobin H disease – (with three genes affected) results in enough alpha protein lacking and excess of beta globins, which leads to the formation of beta globin tetramers called hemoglobin H. These tetramers are more stable and soluble, but under special circumstances can lead to hemolysis, generally shortening the life