

# **Single Nucleotide Polymorphism in the MTHFR Gene and Its Relation to Hypertension in Obese Children**

A Thesis

*Submitted for Partial Fulfillment of the Master's degree in  
Pediatrics*

By

**Mohammed Saad Mohammed El dabbob**

*M.B., B.Ch.*

*Ain Shams University*

Supervised By

**Ass. Prof. Wessam Ahmed Ibrahim Ahmed**

*Assistant Professor of Pediatrics*

*Faculty of Medicine, Ain Shams University*

**Ass. Prof. Alaa Youssef Ahmed**

*Assistant Professor in Pediatrics*

*Faculty of Medicine, Ain Shams University*

**Ass. Prof. Dina Ahmed Soliman**

*Assistant Professor of Clinical and Chemical Pathology*

*Faculty of Medicine, Ain Shams University*

*Faculty of Medicine  
Ain Shams University*

**2018**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا انك لا تعلم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

# Acknowledgment

*Before all, Thanks to **Allah**, The Most Kind  
and The Most Merciful.*

*I would like to express my profound gratitude to **Assistant Prof. Dr. Wessam Ahmed Ibrahim Ahmed**, Assistant Professor of Pediatrics, Faculty of Medicine- Ain Shams University, for her valuable help, assistance, encouragement and supporting me through devoting her time to facilitate the production of this work.*

*Also I'm deeply grateful to **Assistant Prof. Dr. Alaa Youssef Ahmed**, Assistant Professor of Pediatrics, Faculty of Medicine- Ain Shams University, for her most valuable advices and support all through the whole work and for dedicating much of her precious time to accomplish this work. I really have the honor to complete this work under her generous supervision.*

*I am also grateful to **Assistant Prof. Dr. Dina Ahmed Soliman**, Assistant Professor of Clinical Pathology, Faculty of Medicine- Ain Shams University, for her unique effort, considerable help, assistance and knowledge she offered me throughout the performance of this work.*

*Last but not least, I can't forget to thank all members of my **Family**, for pushing me forward in every step in the journey of my life.*

**Mohammed Saad**

# *List of Contents*

Title	Page No.
List of Tables .....	i
List of Figures .....	iii
List of Abbreviations .....	v
Introduction .....	1
Aim of the Work.....	3
Review of Literature	
☞ Hypertension .....	4
☞ Molecular Mechanisms of Hypertension.....	19
☞ Childhood Obesity .....	31
Subjects and Methods .....	60
Results .....	73
Discussion .....	100
Summary .....	107
Conclusion.....	111
Recommendations .....	112
References .....	113
Arabic Summary	

## *List of Tables*

Table No.	Title	Page No.
<b>Table (1):</b>	Pediatric Hypertension: Criteria and Secondary Causes.....	8
<b>Table (2):</b>	Classification of hypertension in children and adolescents, with measurement frequency and therapy recommendations .....	13
<b>Table (3):</b>	Polymorphic Mutations in 5, 10-Methylenetetrahydrofolate Reductase. ....	23
<b>Table (4):</b>	Classification of childhood weight .....	32
<b>Table (5):</b>	Shows the correlation between fluorescence signals and sequences in a sample .....	68
<b>Table (6):</b>	Age data of the studied groups.....	73
<b>Table (7):</b>	Gender distribution of studied groups.....	73
<b>Table (8):</b>	Anthropometric measures of studied groups .....	75
<b>Table (9):</b>	Laboratory characteristics among the studied obese patients .....	76
<b>Table (10):</b>	Fasting lipid profile among the studied obese patients .....	76
<b>Table (11):</b>	Comparison between patients and controls regarding gender distribution .....	78
<b>Table (12):</b>	Comparison between patients and controls regarding age.....	78
<b>Table (13):</b>	Comparison between patients and controls regarding anthropometric measures .....	79
<b>Table (14):</b>	Comparison between patients and controls regarding laboratory data .....	81

## *List of Tables (cont...)*

Table No.	Title	Page No.
<b>Table (15):</b>	Comparison between The genotypic and allelic frequencies among the studied groups [n (%)] .....	82
<b>Table (16):</b>	Correlation between genotype frequency and puberty among the studied groups.....	83
<b>Table (17):</b>	Correlation between genotype frequency and gender among studied groups.....	84
<b>Table (18):</b>	Correlation between blood pressure and gender among studied groups.....	85
<b>Table (19):</b>	Correlation between blood pressure and allele frequency among studied groups .....	86
<b>Table (20):</b>	Correlation between blood pressure and genotype (homozygous and heterozygous) among studied groups .....	88
<b>Table (21):</b>	Correlation between blood pressure and puberty among studied groups.....	90
<b>Table (22):</b>	Comparison between studied groups as regards allele frequency.....	91
<b>Table (23):</b>	Multi-Regression analysis between SBP percentile, onset of obesity and waist height ratio among studied groups: .....	92
<b>Table (24):</b>	Correlation between demographic data and blood pressure among studied groups: .....	93
<b>Table (25):</b>	Correlation between anthropometric measures and blood pressure among studied groups.....	94
<b>Table (26):</b>	Correlation between blood pressure and laboratory data among studied groups.....	95

## *List of Figures*

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Diagnostic testing for mild-to-moderate HTN in children. ....	11
<b>Figure (2):</b>	Pediatric hypertension.....	12
<b>Figure (3):</b>	Work up and treatment of hypertension .....	17
<b>Figure (4):</b>	Homocysteine metabolism .....	22
<b>Figure (5):</b>	Potential mechanisms of homocysteine-induced oxidant stress .....	28
<b>Figure (6):</b>	Prader-Willi syndrome with characteristic facial features; early-childhood onset obesity and short stature .....	34
<b>Figure (7):</b>	Bardet-Biedl syndrome showing central obesity and hypogonadism.....	35
<b>Figure (8):</b>	MOMO syndrome showing macrocephaly, obesity .....	36
<b>Figure (9):</b>	Cohen syndrome showing craniofacial dysmorphism .....	36
<b>Figure (10):</b>	A diagnostic approach to obesity syndromes.....	38
<b>Figure (11):</b>	Medical complication of childhood obesity .....	46
<b>Figure (12):</b>	Gender distribution among studied groups. ....	74
<b>Figure (13):</b>	Correlation between blood pressure and genotype frequency among studied groups. ....	87
<b>Figure (14):</b>	Correlation between blood pressure and genotype (homozygous and heterozygous) among studied groups.....	89

## *List of Figures (cont...)*

Fig. No.	Title	Page No.
<b>Figure (15):</b>	Correlation between blood pressure and puberty among studied groups. ....	90
<b>Figure (16):</b>	Correlation between SBP & Weight. ....	96
<b>Figure (17):</b>	Correlation between SBP & Waist circumference ....	96
<b>Figure (18):</b>	Correlation between SBP & Hip circumference. ....	97
<b>Figure (19):</b>	Correlation between DBP & Weight. ....	97
<b>Figure (20):</b>	Correlation between DBP & Waist circumference. ....	98
<b>Figure (21):</b>	Correlation between DBP & Hip circumference. ....	98
<b>Figure (22):</b>	Correlation between SBP & Fasting insulin. ....	99
<b>Figure (23):</b>	Correlation between DBP & Fasting Insulin. ....	99



## *List of Abbreviations*

<b>Abb.</b>	<b>Full term</b>
<i>AAP</i> .....	<i>American Association of Pediatrics</i>
<i>ACEI</i> .....	<i>Angiotensin Convertase Enzyme Inhibitor</i>
<i>ARBs</i> .....	<i>Angiotensin II Receptor Blockers</i>
<i>ARC</i> .....	<i>Arcuate Nucleus</i>
<i>AS</i> .....	<i>Alstrom Syndrome</i>
<i>BBS</i> .....	<i>Bardet-Biedl Syndrome</i>
<i>BMI</i> .....	<i>BODY MASS Index</i>
<i>BP</i> .....	<i>Blood Pressure</i>
<i>CCBs</i> .....	<i>Calcium Channel Blockers</i>
<i>CCK</i> .....	<i>Cholecystokinin</i>
<i>CHF</i> .....	<i>Congestive Heart Failure</i>
<i>CKD</i> .....	<i>Chronic Kidney Disease</i>
<i>CVD</i> .....	<i>Cardiovascular Disease</i>
<i>DBP</i> .....	<i>Diastolic Blood Pressure</i>
<i>DMH</i> .....	<i>Dorsomedial Nucleus</i>
<i>EPO</i> .....	<i>Erythropoietin</i>
<i>ESRD</i> .....	<i>Ends Stage Renal Disease</i>
<i>FDA</i> .....	<i>Food and Drug Administration</i>
<i>FVa</i> .....	<i>Factor V</i>
<i>GH</i> .....	<i>Growth Hormone</i>
<i>GLP-1</i> .....	<i>Glucagon-Like Peptide</i>
<i>Hcy</i> .....	<i>Homocysteine</i>
<i>HTN</i> .....	<i>Hypertension</i>
<i>IGF-1</i> .....	<i>Insulin Growth Factor 1</i>
<i>LHA</i> .....	<i>Lateral Hypothalamic Area</i>
<i>LVH</i> .....	<i>Left Ventricular Hypertrophy</i>
<i>LVMi</i> .....	<i>Left Ventricular Mass Index</i>
<i>MAOIs</i> .....	<i>Mono Amine Oxidase Inhibitors</i>

## *List of Abbreviations (Cont...)*

<b>Abb.</b>	<b>Full term</b>
<i>MTHFR</i> .....	<i>Methylenetetrahydrofolate Reductase</i>
<i>NHBPEP</i> .....	<i>National High Blood Pressure Education Program</i>
<i>NSAIDs</i> .....	<i>Non Steroidal Anti Inflammatory Drugs</i>
<i>OB</i> .....	<i>Obese</i>
<i>OCP</i> .....	<i>Oral Contraceptive Pills</i>
<i>OW</i> .....	<i>Overweight</i>
<i>PVN</i> .....	<i>Paraventricular Nucleus</i>
<i>QOL</i> .....	<i>Quality of Life</i>
<i>SBP</i> .....	<i>Systolic Blood Pressure</i>
<i>SES</i> .....	<i>Socioeconomic Status</i>
<i>SNP</i> .....	<i>Single Nucleotide Polymorphism</i>
<i>UTI</i> .....	<i>Urinary Tract Infection</i>
<i>VLEDs</i> .....	<i>Very Low Energy Diets</i>
<i>VMH</i> .....	<i>Ventromedial Hypothalamic Nucleus</i>

# ABSTRACT

Our study revealed a highly statistically significant positive correlation between hypertension and MTHFR gene SNP.

Regarding the C667T polymorphism, a higher frequency was detected among obese hypertensive children (60%) than obese normotensive children (26.7%) with a highly significant difference between them ( $p=0.009$ ).

Genotypic analysis of the cases regarding C667T MTHFR revealed that 25 patients (35.7%) had genotype (CC), While 45 patients (64.3%) had mutant type, and 42 of them (60%) were heterozygous genotype (CT) and 3 (4.3%) were homozygous genotype (TT).

**Keywords:** Bardet-Biedl Syndrome - Angiotensin II Receptor Blockers - Congestive Heart Failure

## INTRODUCTION

In the past 2 decades there has been increased recognition of the importance of blood pressure (BP) measurement in the pediatric population particularly in relation to the rising prevalence of childhood obesity. However, the importance of high BP goes beyond its relation to obesity, because longitudinal studies reveal a relation between childhood BP and future cardiovascular risk factors in young adults, independent of body mass index (BMI) (*LO et al., 2013*).

The relationship between obesity and hypertension is well recognized. Overweight and obesity increase the risk of elevated blood pressure. The prevalence of hypertension was 2 to 6 fold higher in obesity than in normal weight crowd (*Yin et al., 2012*).

The prevalence of childhood obesity has increased markedly over the last 2 decades. This increase is associated with an increase in hypertension rates which could lead to atherosclerotic disease in adulthood. Primary hypertension in children has become increasingly common in association with other cardiovascular risk factors that include being overweight, insulin resistance, and dyslipidemia (*Abolfotouh et al., 2011*).

Methylenetetrahydrofolatereductase (MTHFR) is one of the key enzymes in folate metabolism that is essential for numerous cellular functions. The C677T polymorphism in the

coding region of human MTHFR gene that changes an alanine to a valine residue is a common single nucleotide polymorphism (SNP). Its polymorphic distribution varies greatly in different populations. This gene variant encodes a thermolabile form of MTHFR, which decreases the enzyme activity by approximately 35% in heterozygote (CT) and 70% in mutant homozygote (TT). The homozygous C667T in the MTHFR gene is reported to be associated with the risk of certain human diseases, including some cardiovascular disorders, cancers and neural tube defects (*Yang et al., 2007*).

## **AIM OF THE WORK**

**T**o assess the relationship between MTHFR gene polymorphisms and hypertension in obese children.

## Chapter 1

# HYPERTENSION

**H**ypertension is a major long-term health condition and is the leading cause of premature death among adults throughout the world, including both developed, developing, and lesser developed countries. Primary hypertension emerges from a complex inter-play of genetic, environmental, and behavioral factors. Owing to the hereditary component of hypertension, the disorder is considered to have its origins in the young. It is now established that hypertension is detectable in children and adolescents and is not uncommon (*Falkner, 2010*).

Obesity and hypertension are both common health problems in children and adolescents and, in concert with the increasing prevalence of obesity in children; pediatric hypertension has undergone an epidemiological shift. Among all the demographic and clinical factors analyzed, body mass index (BMI) has been most strongly associated with hypertension. Several studies have reported positive associations between obesity and elevated blood pressure and childhood obesity is often associated with the future development of hypertension (*Zhang, 2011*).

### **Definition:**

Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) that is greater than or equal to the 95th percentile for sex, age, and