

Study of Methylenetetrahydrofolate Reductase Gene Polymorphism in Children with Conotruncal Heart Defects and Their Mothers

Thesis

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By

Ali Mohammad Ali Elnashar

M.B., B.Ch.

Faculty of Medicine – Ain Shams University

Under Supervision Of

Prof. Dr. Alyaa Amal Kotby

Professor of Pediatrics

Faculty of Medicine-Ain Shams University

Prof. Dr. Nagwa Abdel Meguid Mohamed

Professor of Human Genetics

National Research Center

Dr. Ola Abd El-Aziz Elmasry

Assistant Professor of Pediatrics

Faculty of Medicine-Ain Shams University

**Faculty of medicine
Ain Shams University
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List of Tables

Table No.	Title	Page No.
Table (1):	Frequency of different types of CHD	10
Table (2):	Chromosomal abnormality syndromes associated with congenital heart defects:	54
Table (3):	Descriptive analysis of the study population.	104
Table (4):	Cardiac Diagnosis of the Patients group.....	105
Table (5):	Comparison between patients and control group as regards methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms at exon 4.	108
Table (6):	Comparison between patients and control group as regards maternal MTHFR gene polymorphisms at exon4.....	110
Table (7):	Comparison between patients and control group as regards MTHFR gene polymorphisms at exon 7.....	112
Table (8):	comparison between patients and control group as regards maternal MTHFR gene polymorphisms at exon7.....	114

List of Figures

Figure No.	Title	Page No.
Fig. (1):	Primitive heart tube.	5
Fig. (2):	Looping of primitive heart tube.....	5
Fig. (3):	Diagrammatic representation of outflow tract septation and final septation of the ventricles and atrioventricular canal.....	7
Fig. (4):	Schematic representation of various congenital heart defects that result from abnormalities in conotruncal rotation.....	7
Fig. (5):	Shows aortic arch development, giving rise to all arterial system. Embryologically, 6 paired pharyngeal arteries was connecting trunco-aortic sac to the paired dorsal aortae.	9
Fig. (6):	TOF morphology compared to normal heart.....	12
Fig. (7):	Children with Tetralogy of Fallot exhibit marked cyanosis during hypercyanotic episode.....	19
Fig. (8):	D-transposition of the great arteries	25
Fig. (9):	Normal heart and DORV heart.....	32
Fig. (10):	Truncus Arteriosus.....	37
Fig. (11):	Anatomic subtypes of truncus arteriosus (TA), according to the classification systems of both Collett and Edwards (I, II, III) and the Van Praaghs (A1, A2, A3, A4)	38
Fig. (12):	Normal pulmonary valve and stenotic pulmonary valve.....	44
Fig. (13):	Simplified folate metabolism indicating its one-carbon donors and acceptors involved in methyl-group biogenesis, thymidylate synthesis and purine synthesis.....	67

List of Figures (Cont...)

Figure No.	Title	Page No.
Fig. (14):	Human MTHFR Gene is on chromosome (1). It's position shown as an arrow.	69
Fig. (15):	An example of 2D imaging:	83
Fig. (16):	Represents distribution of CHD among population study.....	105
Fig (17):	Agarose gel electrophoresis of digested PCR product of exon (4) of maternal MTHFR gene.....	106
Fig (18):	Mutational analysis of MTHFR 1298 polymorphism in exon (7).....	107
Fig. (19):	Comparison between patients and control group as regards methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms at exon 4.....	109
Fig. (20):	Comparison between patients and control group as regards maternal MTHFR gene polymorphisms at exon4.	111
Fig. (21):	Comparison between patients and control group as regards MTHFR gene polymorphisms at exon 7.	113
Fig. (22):	Comparison between patients and control group as regards maternal MTHFR gene polymorphisms at exon7.	115

List Of Abbreviations

A:	Adenine
APS:	Ammonium per sulphate
AR:	Autosomal resessive
AS:	Aortic Stenosis
ASCA:	Aberrant subclavian artery
ASD:	Atriale Septal Defect
AVC:	Atrioventricular canal
AVSD:	Artrioventricular septal defect
BAS:	Ballon atrial septostomy
BAV:	Bicuspid aortic valve
Bp:	Base pair
C:	Cytosine
CH3-B12:	Ethylcobalamin
CHDs:	Congenital heart defects
CHF:	Congestive Heart Failure
CNS:	Central nervous system
CRS:	Congenital rubella syndrome
CT:	Computed Tomography
CTDs:	Conotruncal defects
CXR:	Chest X-rays
DCM:	Dilated cardiomyopathy
DHF:	Dihydrofolate
DNTPs:	Deoxynucleotide triphosphates

DORV:	Double Outlet Right Ventricle
DORV:	Double-outlet right ventricle
dTMP:	Deoxythymidine-5'-phosphate
dUMP:	Deoxyuridine-5'-phosphate
ECG:	Electrocardiogram
F:	Folate
FAVS:	Facioauriculovertebral spectrum
FH4 :	Tetrahydrofolate
G:	Guanine
GI:	Gastrointestinal
GU:	Genitourinary
HCM:	Hypertrophic cardiomyopathy
HLHS:	Hypoplastic left heart syndrome
IAA:	Interrupted aortic arch
LVOTO:	Left ventricular outflow tract obstruction
Mgcl:	Magnesium Chloride
MRI:	Magnetic Resonance Imaging
MS:	Mitral stenosis
MTHFR:	Methylenetetrahydrofolate reductase
MVP:	Mitral valve Prolapse
Nacl:	Sodium Chloride
OD:	Optical Density
OMIM:	Online Mendelian inheritance of man
PA:	Pulmonary atresia
PAPVC:	Partial anomalous pulmonary venous connection

PCR:	Polymerase chain reaction
PDA:	Patent Ductus Arteriosus
PFO:	Patent Foramen Oval
PGE1:	Prostaglandine E1
PKU:	Phenylketonuria
PS (V):	Pulmonary stenosis (valvar specified)
PS:	Pulmonic stenosis
RDA:	Recommended dietary allowance
RVOTO:	Right ventricular outflow tract obstruction
S2:	Second heart sound:
SNPS:	Single nucleotide polymorphisms
SVC:	Superior vena cava
T:	Thymine
TAVPC:	Total anomalous pulmonary venous connection
TEMED:	Tetramethylethylenediamin
TGA:	Transpoition of great arteries
TGV:	Transposition of the great vessels
THF:	Tetrahydrofolate
TOF:	Tetralogy of Fallot
TV:	Tricusbid valve
UV:	Ultra Violet
VSD:	Ventricular septal defect
2D:	Two-dimensional
5, 10-CH ₂ -THF:	5, 10-methylenetetrahydrofolate
5-CH ₃ -THF:	5-methyltetrahydrofolate

List of Contents

Title	Page No.
List of Tables	i
List of Figures.....	ii
List of Abbreviations	iv
Introduction.....	1
Aim of the work.....	3
Review of literature	
♦ Congenital Heart Defects and Conotruncal Heart Defects	4
♦ Etiology of Congenital Heart Defects.....	53
♦ Folic Acid and Methylenetetrahydrofolate Gene Polymorphism.....	64
Patient and methods	79
Results	104
Discussion.....	116
Summary and conclusion	129
Recommendation.....	132
References	133
Arabic Summary	

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Introduction

Congenital heart defects (CHDs) are the most common structural birth defects, affecting about 8 to 10 of every 1000 live birth. The etiology of non-syndromic CHD is complex, involving both genetic and environmental risk factors (*Botto and Correa, 2003*).

Conotruncal heart defects (outflow tract defect) are a serious subset of CHD with prevalence rate about 8 per 10,000 live births. Common types are tetralogy of Fallot (TOF), transposition of great arteries (TGA), truncus arteriosus, double outlet right ventricle, interrupted aortic arch and pulmonary stenosis. All defects cause improper circulation of oxygenated and deoxygenated blood (*Botto et al., 2001*).

The association between periconceptional folic acid use and a reduced risk of fetal conotruncal cardiac defects has been reported in a number of case-control studies (*Storti et al., 2003 and Shaw et al., 2005*). It is widely accepted that the impact of folic acid intake on pregnancy outcome is modified by variants in both maternal and fetal genes that code for critical enzymes in the folate and homocysteine pathways (*Doolin et al., 2002*).

The 5,10-methylenetetrahydrofolate reductase (MTHFR) gene is located on chromosome 1 at 1p36.3. The complementary DNA sequence is 2.2 kilobases long and consists of 11 exons. Methylenetetrahydrofolate reductase (MTHFR) catalyses the biologically irreversible reduction of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the methyl donor for methionine synthesis from homocysteine (*Goyette et al., 1998*). Two single nucleotide polymorphisms (SNPs) in MTHFR, 677C-T (exon 4) and 1298A-C (exon 7) are associated with decreased enzyme activity (*Botto and Yang, 2000*).

Few studies have investigated the association between MTHFR genotypes and the risk of development of congenital anomalies. Down syndrome, oral clefts, urogenital anomalies and limb defects occur with reduced incidence among folic acid users (*Hall and Solehdin, 1998 and Zhu et al., 2006*). Recent studies have found an association between conotruncal heart defect and maternal and offspring MTHFR gene polymorphism. This suggests that such an investigation might yield valuable data (*Van Beynum et al., 2006 Goldmuntz et al., 2008*).

Aim of the Work

The present work aims at studying the association between conotruncal heart defects and maternal and infant methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms.

Congenital Heart Defects

Congenital heart defects (CHDs) refer to any abnormality in the cardio circulatory structure or function that is present at birth even if it is discovered later (*National Institute of Health, 2006*).

CHDs are among the most common congenital malformations in new borns representing 25% of all congenital malformations. They comprise about eight percent of all deaths during the first year of life and account for about third of infant deaths due to birth defects (*Baily and Berry, 2005*).

Heart Development:

Heart development begins at 3rd to 4th weeks of gestation by folding of the embryo. The two heart tubes are fused together to form the primitive heart which consists of four connected chambers, bolbus cordis, primitive ventricle, primitive atrium and sinus venosus (*Emmanouilides, 2008*).

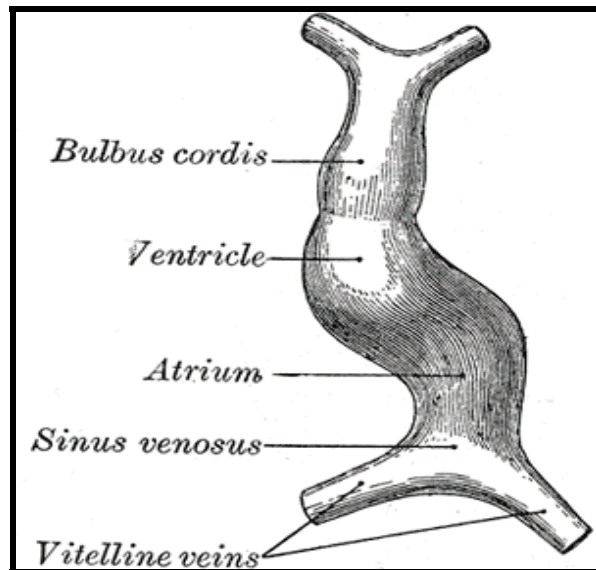


Fig. (1): Primitive heart tube.

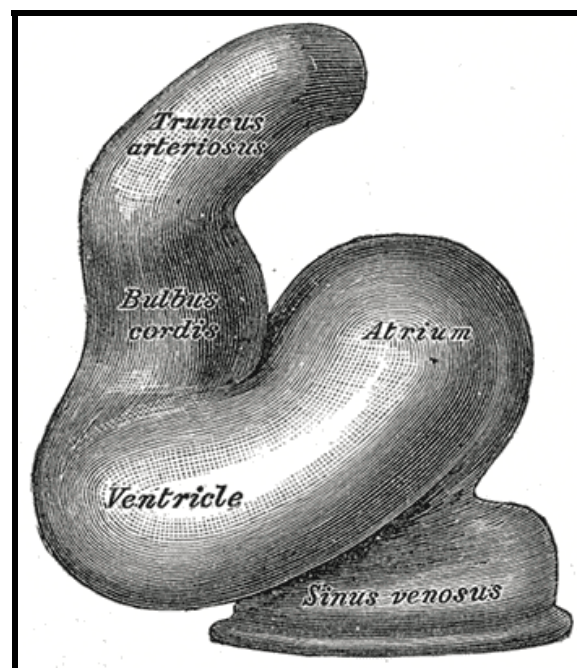


Fig. (2): Looping of primitive heart tube.

http://en.wikipedia.org/wiki/Category:Gray_Anatomy_images

Conotruncal development

Normal development of the conotruncus involves proper septation and alignment of the pulmonary and aortic outflow tracts above their respective ventricles. The embryologic precursors to the ventricular outflow tracts and great arteries are the distal bulbus cordis and truncus arteriosus, respectively. The anatomic transition point, between the bulbus cordis and truncus arteriosus, coincides with the level at which the semilunar valves form from the growth and fusion of the truncal-bulbar cushions. This region encompassing the distal bulbus cordis and truncus arteriosus will be referred to, as the conotruncus (*McElhinney et al., 2001*).

The conotruncus, in normal development, is initially rightwardly situated over the embryologic right ventricle. This region undergoes a spatially complex process of rotation, septation, and differential cell growth and death that results in the proper alignment of the outlet septum with the ventricular trabecular septum. The transition between these two structures is ultimately spanned and closed by the membranous septum.