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

Thesis

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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:	Magnisuim Chloride
MRI:	Magnetic Resonance Imaging
MS:	Mitral stenosis
MTHFR:	Methylenetetrahydrofolate reductase
MVP:	Mitral valve Prolapse
Nacl:	Sodium Chloride
OD:	Optical Density
OMIM:	On line Mendelian inheritance of man
PA:	Pulmonary atresia
PAPVC:	Partial anomalous pulmonary venous connection

PCR: Polymerase chain reaction

PDA: Patent Ductus Arteriosis

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-CH2-THF: 5, 10-methylenetetrahydrofolate

5-CH3-THF: 5-methyltetrahydrofolate

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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. Methylenetetra-hydrofolate reductase (MTHFR) catalyses the biologically irreversible reduction of 5, 10-methylenetetra-hydrofolate 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).***

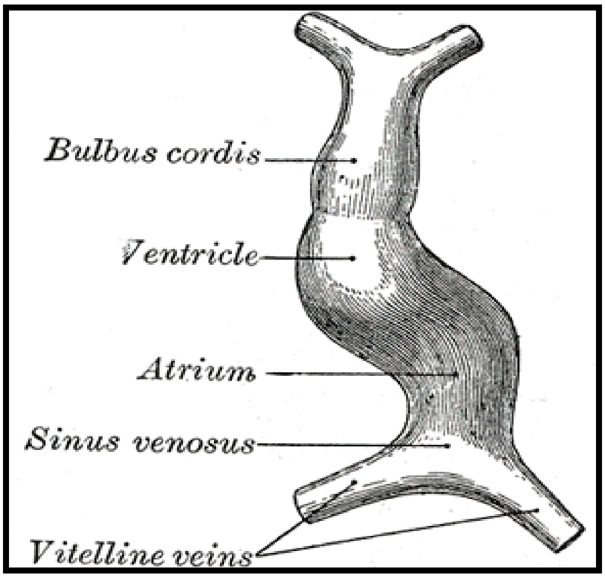

Fig. (1): Primitive heart tube.

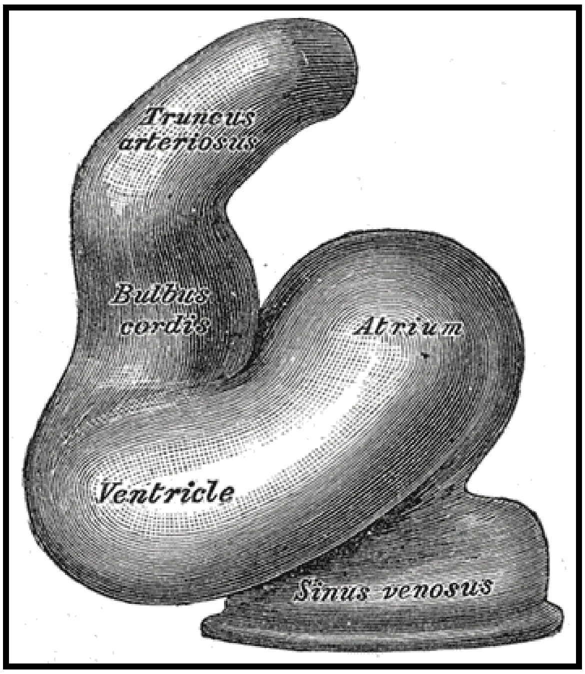

Fig. (2): Looping of primitive heart tube.

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.