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Original Article

Relationship of the MTHFD1 (rs2236225), eNOS (rs1799983), CBS (rs2850144) and ACE (rs4343) gene polymorphisms in a population of Iranian pediatric patients with congenital heart defects

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Abstract Congenital heart defects are structural cardiovascular malformations that arise from abnormal formation of the heart or major blood vessels during the fetal period. To investigate the association of 4 single nucleotide polymorphisms (SNPs) in the *MTHFD1*, *eNOS*, *CBS* and *ACE* genes, we evaluated their relationship with CHD in Iranian patients. In this case–control study, a total of 102 children with CHD and 98 control children were enrolled. Four SNPs including MTHFD1 G1958A, eNOS G894T, CBS C-4673G and ACE A2350G were genotyped by PCR-SSCP, Multiplex ARMS PCR and PCR-RFLP methods and confirmed by direct sequencing. We genotyped 102 patients and 98 controls for four polymorphisms by statistically analysis. There were three SNPs including MTHFD1 G1958A, eNOS G894T and ACE A2350G which might increase the risk of CHD, but CBS C-4673G was not significantly different between patients and controls. ($P = 0.017$, $P = 0.048$, $P = 0.025$ and $P = 0.081$ respectively). The allele frequencies of three SNPs for MTHFD1 G1958A, eNOS G894T and ACE A2350G in CHD are higher than that in control. Our results show that there is a significant relationship between MTHFD1 G1958A, eNOS G894T and ACE A2350G polymorphisms with CHD. Therefore, The AA and GA genotypes of MTHFD1 G1958A, TT and GT genotypes of eNOS G894T and the AA and GA genotypes of *ACE* A2350G are susceptible factors for CHD and may increase the risk of CHD.
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Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Congenital heart defects are serious and common conditions that caused by abnormal formation of the heart during fetal development and have significant impact on morbidity, mortality, and healthcare costs in children and adults [1]. The most commonly reported incidence of congenital heart defects is between 9.3 per 1000 live births in Asia [2]. Of these, about 25% require invasive treatment in the first year, which imposes significant economic problems to the society and the families. It is generally agreed that the CHD is caused by both genetic and environmental risk factors, though the etiology of CHD is not entirely clear [3].

Genetic abnormalities such as chromosomal defects and single-gene disorders appear to be the major causes of CHD, but determining accurate causes of heart defects is challenging, principally because CHD is a complex genetic trait [4]. Mainly because of recent developments in new genomic technology such as next-generation DNA sequencing, researchers have begun to identify a wide variety of genetic polymorphisms in CHD. Epidemiological investigations have revealed that sufficient maternal folate supplementation in early pregnancy could decrease the incidence of CHD in fetus [5].

Therefore, folate-dependent enzymes, such as 5,10-methylenetetrahydrofolate dehydrogenase (MTHFD1) and cystathionine beta-synthase (CBS) which have central role in folate and homocysteine metabolism, are attractive candidate genes in CHD [6].

In addition, endothelial NO synthase (eNOS) enzyme is expressed during the early stages of cardiogenesis and plays an essential role in normal heart development [7]. Also, the angiotensin-converting enzyme (ACE) is responsible for the conversion of angiotensin I into angiotensin II, the main hormone of the renin–angiotensin system (RAS). This conversion changes permeability of ion channels in cell membrane and increases oxidative stress. It is proven that Angiotensin II has directly effects on the heart tissue: It stimulates myocardial cells growth by increasing the protein synthesis and increasing the peripheral cardiovascular rigidity [8]. Single nucleotide polymorphisms (SNPs) in genes encoding these enzymes could be research hotspots of genetic susceptible factors for CHD, such as MTHFD1 G1958A, eNOS G894T, CBS C-4673G and ACE A2350G. To date, several studies focusing on the association between these polymorphisms and risk of CHD have been reported [9,10]. But, the conclusions of the studies are conflicting and depending on small sample size of individual studies and geographic differences. Present study investigated whether there is an association between CHD and the 4 SNPs distributed in MTHFD1, eNOS, CBS and ACE genes in an Iranian case–control cohort.

Materials and methods

Patients

In this case–control study, we enrolled 102 unrelated pediatric patients with congenital heart defects who referred to the Department of Cardiac Surgery in Afshar hospital (Yazd, Iran) from 2012 to 2016. All the samples were obtained from the infants diagnosed as CHD and were confirmed by both diagnostic procedures such as echocardiogram and cardiac catheterization and subsequent anatomy at the time of surgery. Also, 98 unrelated healthy infants (59 males and 39 females) were born in this center at the same period, were selected randomly and enrolled into the control group. There were no differences in age, sex, and ethnicity in patients compared with healthy cases. In total, 102 individuals with CHD were available for study after clinical diagnosis. There were no significant differences in the baseline characteristics between the patient and control groups (Table 1). Of the all patients included in the study, 56 (54.9%) were male. The mean age at assessment was 2.5 ± 0.6 years (range 0–3.8 years). Of these, 63 subjects (61.76%) had perimembranous ventricular septal defect (VSD), 24 (23.52%) suffered from secundum atrial septal defect (ASD), and 15 (14.70%) had Tetralogy of Fallot (TOF). Written consent was obtained from all research participants and the laboratory protocols in this study were approved by the institutional ethics boards of the Yazd University. Genomic DNA was extracted from 5 mL peripheral blood leukocytes using a DNA isolation kit (Qiagen Co, Tehran, Iran). Samples were stored at −20 °C until their use.

Determination of genotypes

Four SNPs of genes involved in folate metabolism (MTHFD1 and CBS) and endothelial NO synthase and angiotensin-converting enzyme (ACE) were detected by PCR-RFLP,

Table 1 Baseline characteristics of case and control groups.

Characteristics	Case group (N = 102)	Control group (N = 98)	*P*-value
Age at enrollment (years)	2.5 ± 0.6 (0–3.8)	2.3 ± 0.5 (0–4.1)	0.75
Gender			
Male	56 (54.9%)	59 (60.2%)	0.64
Female	46 (45.1%)	39 (39.8%)	
Mother's age (years)	29.30 ± 6.71	28.17 ± 6.19	0.09
Gestational age (week)	34.87 ± 6.54	38.56 ± 3.68	0.001
Birth weight (gr)	2539.78 ± 981.87	3198.73 ± 759.42	0.004
Mother's weight (kg)	73.72 ± 15.65	76.12 ± 14.4	0.21
Cesarean section delivery (%)	62 (60.7%)	59 (60.2%)	0.92

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