MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3536-3539
DOI: 10.12659/MSM.894830

Received: 2015.05.29
Accepted: 2015.07.14
Published: 2015.11.16

Association Between *DSCR1* Variations and Congenital Heart Disease Susceptibility

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABD Ren Yu Guo
BCD Xiao Feng Li
DEF Song Bai
BE Jian Guo
CD Nan Ding
CFG Zhong Zhi Li

Cardiac Center, Beijing Children's Hospital affiliated to Capital Medical University, Beijing, P.R. China

Corresponding Author: ZhongZhi Li, e-mail: zhongzhili1946@126.com
Source of support: Departmental sources

Background: The objective of this study was aimed to detect the association of Down syndrome critical region 1 (*DSCR1*) gene polymorphisms (rs149048873 and rs143081213) and congenital heart disease (CHD) susceptibility.

Material/Methods: This case-control study included 102 CHD patients and 113 healthy controls. Cases and controls were matched in age and gender. Genotypes of *DSCR1* gene polymorphisms were detected by TaqMan method in cases and controls. Hardy-Weinberg equilibrium (HWE) examination was performed by PLINK 1.0 software. Chi square test was utilized to assess the distribution of the genotypes and the alleles. Relative risk of CHD was presented by odds ratios (ORs) with 95% confidence intervals (CIs). All of the calculations were implemented using SPSS 18.0.

Results: Variant genotype distribution of rs149048873 and rs143081213 mutations were higher in cases than in controls, but the differences were not statistically obvious ($P>0.05$). Additionally, frequencies of mutant allele of the two polymorphisms were also significantly different in case and control groups ($P>0.05$).

Conclusions: No significant associations existed between *DSCR1* gene rs149048873 and rs143081213 polymorphisms and CHD susceptibility.

MeSH Keywords: **Genes, vif • Heart Defects, Congenital • Polymorphism, Single Nucleotide**

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894830

1181 1 — 28

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Congenital heart disease (CHD) refers to defects in heart and vessel structure which exist from birth. CHD is the most common type of congenital deformities and one of the leading birth defects related to deaths. Incidence of this disease in China was about 8/1000 in the past few years [1], and the morbidity presents an upward trend in recent years. CHD could be classified into various types, and its symptoms are related to the types. Among other symptoms, CHD frequently presents shortness of breath for some patients in early stage while others may express no sign throughout their lives.

CHD may be caused by genetic or environmental factors, but is usually a combination of the two sides [2–7]. It has been recognized that multiple environmental factors can increase the CHD risk through their influences on gravida during pregnancy, such as viral infection, chemical, and maternal diseases [8–11]. But not all pregnant women who expose to risk factors bear CHD infants, indicating there are differences in individual susceptibility which is determined by hereditary factors. So it is believed that the main causes of CHD embrace genetic changes, including focal mutation, deletion or insertion of DNA and chromosomal abnormalities [12]. Locating at chromosome 21, down syndrome critical region-1 (*DSCR1*, also known as *RCAN1*) gene is implicated in the structure of fetal heart [13]. It is speculated that single nucleotide polymorphisms (SNPs) of *DSCR1* gene might play potential roles in the occurrence of CHD.

In this study, we compared the genotype distribution of the *DSCR1* gene polymorphisms (rs149048873 and rs143081213) in CHD patients and healthy controls. The association between the *DSCR1* gene polymorphisms and CHD susceptibility were detected in Chinese Han population.

Material and Methods

Subjects

In this case-control study, case group comprised 102 children with CHD who were hospitalized in Beijing Children's Hospital affiliated to Capital Medical University from JAN 2012 to JAN 2015. The healthy controls were recruited from Beijing region. Controls were matched with cases in age and gender. All of the subjects were 0–11 years old and unrelated Chinese Han people. Written informed consents were signed by the children's parents. This study was approved by the ethic committee of Beijing Children's Hospital affiliated to Capital Medical University.

Genotyping method

Genomic DNA was extracted from 1ml fasting venous blood using TIANamp Blood DNA Kit (TIANGEN, China). Genotype distribution of *DSCR1* gene polymorphisms (rs149048873 and rs143081213) were detected by TaqMan probe assay method using ABI PRISM 7700 system (Applied Biosystems, USA).

Statistical analysis

Hardy-Weinberg equilibrium (HWE) examination was performed by PLINK 1.0 software. SPSS 18.0 were used to conduct statistical analysis. $P<0.05$ is considered statistical significance. The differences of genotype and allele distribution between case and control groups were assessed by Chi square test. Odds ratios (ORs) with 95% confidence intervals (CIs) were utilized to present the relative risk of CHD.

Results

HWE examination

Genotype and allele distribution of rs149048873 and rs143081213 variants of *DSCR1* gene were in accordance with HWE in both case and control groups ($P>0.05$), indicating the representativeness of the subjects.

Association of DSCR1 gene rs149048873 and rs143081213 variations with CHD risk

The frequencies of the genotypes and alleles of the two variations were compared between the case and control groups (Table 1). Variant genotypes AA and AA in rs149048873 and rs143081213 respectively were more frequent in case group than in control group. But the difference of the frequencies was not significant ($P>0.05$). Frequencies of rs149048873 A allele and rs143081213 A allele in cases were 9.31% and 6.86% respectively, and were higher than that in controls. No significant difference, however, was observed in the two allele between case and control groups ($P>0.05$).

Discussion

CHD is defined as a gross structural abnormality of the heart or great vessels in actually (or potentially) functional significance. As the most common defect among birth defects, CHD is one of the leading causes of noninfectious death in the first year of neonates [14]. In 2000 CHD was provided a generic classification system. For some types of CHD, no symptom was detected throughout whole life. Unfortunately, most CHD cases develop the disease in their early lives. With the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Genotype distribution of *DSCR1* gene rs149048873 and rs143081213 polymorphisms.

SNP	Case n=102 (%)	Control n=113 (%)	*P*	OR (95%CI)
rs149048873				
GG	84 (82.35)	99 (87.61)	–	–
GA	17 (16.67)	13 (11.50)	0.274	1.541 (0.708–3.357)
AA	1 (0.98)	1 (0.89)	0.908	1.179 (0.073–19.131)
G	185 (96.69)	211 (93.36)	–	–
A	19 (9.31)	15 (6.64)	0.304	1.445 (0.714–2.924)
rs143081213				
GG	89 (87.25)	101 (89.38)	–	–
GA	12 (11.76)	11 (9.73)	0.629	1.238 (0.521–2.944)
AA	1 (0.98)	1 (0.89)	0.929	1.135 (0.070–18.410)
G	190 (93.14)	213 (94.25)	–	–
A	14 (6.86)	13 (5.75)	0.635	1.207 (0.554–2.633)

improvement of medical standards, the quantity of preterm infant is increasing, and so is the incidence of CHD. The mortality of the disease, however, shows a downward tendency [15]. Occasionally, the situations in a small part of CHD patients could improve without treatment. Mild abnormalities in patients having no obvious obstacle in circulatory function do not require any treatment. CHD is generally serious and requires to be treated through surgery and/or medications. CHD creates huge economic burdens to family and society. Early diagnosis and suitable treatment for CHD could increase the survival rate and achieve good prognosis. The exploration on CHD etiology will contribute to the diagnosis of it. Previous studies found that CHD is a complex disease, and affected by gene and environment factors [16-18]. However, the pathogenesis of CHD is still unclear.

To date, several studies have investigated the pathogenic genes of CHD [19–21]. It is reported that *DSCR1* gene is related to cardiogenesis [22–24]. Protein encoded by *DSCR1* gene is a regulator of calcineurin 1, and inhibits the genetic transcription of the calcineurin-dependent signaling pathways. The expression of *DSCR1* gene is mainly detected in the heart and central nervous system in embryos [22]. This gene is located in chromosome 21q22.12, and contains 9 exons. It has been revealed that a regulatory sequence in the promoter region of human *DSCR1* gene could alter the expression of the gene [24]. *DSCR1* gene is associated with many diseases [25–28], including CHD. Polymorphisms of the gene might play potential roles in the expression of the gene, and contribute to the occurrence and development of many diseases. rs149048873 and rs143081213, the two SNPs in the promoter region of *DSCR1* gene, may change the expression of this gene, and then affect the occurrence of CHD. However, there were few studies focusing on relationship of these polymorphisms with the occurrence of CHD.

So we explored the association between *DSCR1* gene polymorphisms (rs149048873 and rs143081213) and the susceptibility of CHD in this study through detecting the distribution of the genotypes and alleles of the two SNPs in case and control groups. Even though distribution of the variant genotypes mutations was higher in cases than in controls, no significant difference was found between the two groups. Similar results were observed in the variant alleles. Frequencies of A and A alleles in the polymorphisms rs149048873 and rs143081213 respectively were 9.31% and 6.86% in cases, and higher than in controls (about 2.67% and 1.11%). The differences still were not significant. These results were identical with those from previous study which conducted in sporadic CHD [28]. Our study suggested that *DSCR1* gene rs149048873 and rs143081213 polymorphisms had no significant association with the CHD risk.

Conclusions

Although the subjects were representative, there still existed many limitations in our study, including small sample size and unadjusted results. Therefore, well designed multiple-center studies need to be carried out in the future to obtain more effective evidence to clarify the etiology of CHD.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

References:

1. Yang XY, Li XF, Lu XD, Liu YL: Incidence of congenital heart disease in Beijing, China. Chin Med J (Engl), 2009; 122: 1128–32
2. Wang F, Zhou S, Wang Y et al: Association of DNMT1 gene polymorphisms with congenital heart disease in child patients. Pediatr Cardiol, 2015; 36: 906–11
3. Aburawi EH, Aburawi HE, Bagnall KM, Bhuiyan ZA: Molecular insight into heart development and congenital heart disease: An update review from the Arab countries. Trends Cardiovasc Med, 2015; 25: 291–301
4. Correa A, Levis DM, Tinker SC, Cragan JD: Maternal cigarette smoking and congenital heart defects. J Pediatr, 2015; 166: 801–4
5. Dulfer K, Duppen N, Blom NA et al: Effect of exercise training on sports enjoyment and leisure-time spending in adolescents with complex congenital heart disease: the moderating effect of health behavior and disease knowledge. Congenit Heart Dis, 2014; 9: 415–23
6. Zhang X, Li S, Wu S et al: Prevalence of birth defects and risk-factor analysis from a population-based survey in Inner Mongolia, China. BMC Pediatr, 2012; 12: 125
7. Wang X, Li P, Chen S et al: Influence of genes and the environment in familial congenital heart defects. Mol Med Rep, 2014; 9: 695–700
8. Blue GM, Kirk EP, Sholler GF et al: Congenital heart disease: current knowledge about causes and inheritance. Med J Aust, 2012; 197: 155–59
9. Huhta J, Linask KK: Environmental origins of congenital heart disease: the heart-placenta connection. Semin Fetal Neonatal Med, 2013; 18: 245–50
10. Tikkanen J, Heinonen OP: Congenital heart disease in the offspring and maternal habits and home exposures during pregnancy. Teratology, 1992; 46: 447–54
11. Zierler S, Rothman KJ: Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. N Engl J Med, 1985; 313: 347–52
12. Thienpont B, Mertens L, de Ravel T et al: Submicroscopic chromosomal imbalances detected by array-CGH are a frequent cause of congenital heart defects in selected patients. Eur Heart J, 2007; 28: 2778–84
13. Fuentes JJ, Pritchard MA, Planas AM et al: A new human gene from the Down syndrome critical region encodes a proline-rich protein highly expressed in fetal brain and heart. Hum Mol Genet, 1995; 4: 1935–44
14. Hoffman JI, Kaplan S: The incidence of congenital heart disease. J Am Coll Cardiol, 2002; 39: 1890–900
15. Lozano R, Naghavi M, Foreman K et al: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet, 2012; 380: 2095–128
16. Li X, Sundquist J, Hamano T et al: Neighbourhood deprivation, individual-level and familial-level socio-demographic factors and risk of congenital heart disease: A nationwide study from Sweden. Int J Behav Med 2015 [Epub ahead of print]
17. Schulkey CE, Regmi SD, Magnan RA et al: The maternal-age-associated risk of congenital heart disease is modifiable. Nature, 2015; 520: 230–33
18. Tamayo C, Manlhiot C, Patterson K et al: Longitudinal evaluation of the prevalence of overweight/obesity in children with congenital heart disease. Can J Cardiol, 2015; 31: 117–23
19. El Malti R, Liu H, Doray B et al: A systematic variant screening in familial cases of congenital heart defects demonstrates the usefulness of molecular genetics in this field. Eur J Hum Genet, 2015 [Epub ahead of print]
20. Pan Y, Wang ZG, Liu XY et al: A Novel TBX1 loss-of-function mutation associated with congenital heart disease. Pediatr Cardiol, 2015 [Epub ahead of print]
21. Burger NB, Bekker MN, de Groot CJ et al: Why increased nuchal translucency is associated with congenital heart disease: a systematic review on genetic mechanisms. Prenat Diagn, 2015; 35(6): 517–28
22. Casas C, Martinez S, Pritchard MA et al: Dscr1, a novel endogenous inhibitor of calcineurin signaling, is expressed in the primitive ventricle of the heart and during neurogenesis. Mech Dev, 2001; 101: 289–92
23. Wang Y, De Keulenaer GW, Weinberg EO et al: Direct biomechanical induction of endogenous calcineurin inhibitor Down Syndrome Critical Region-1 in cardiac myocytes. Am J Physiol Heart Circ Physiol, 2002; 283: H533–39
24. Wu H, Kao SC, Barrientos T et al: Down syndrome critical region-1 is a transcriptional target of nuclear factor of activated T cells-c1 within the endocardium during heart development. J Biol Chem, 2007; 282: 30673–79
25. Martin KR, Corlett A, Dubach D et al: Over-expression of RCAN1 causes Down syndrome-like hippocampal deficits that alter learning and memory. Hum Mol Genet, 2012; 21: 3025–4.
26. Roselli F: Down syndrome DSCR1 causes spine pathology via the Fragile X-related protein FMRP. EMBO J, 2012; 31: 3647–49
27. Lin KG, Tang M, Guo YB et al: Two polymorphisms of RCAN1 gene associated with Alzheimer's disease in the Chinese Han population. East Asian Arch Psychiatry, 2011; 21: 79–84
28. Li X, Wang G, An Y et al: Association between sequence variations in RCAN1 promoter and the risk of sporadic congenital heart disease in a Chinese population. Pediatr Cardiol, 2015 [Epub ahead of print]

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]