Variants of resistin gene and the risk of idiopathic dilated cardiomyopathy in Pakistan

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ABSTRACT

Background: In cardiovascular disease phenotypes, a genetic factor is an important determinant of both familial and non-familial dilated cardiomyopathies. Resistin is a novel adipocyte derived peptide, associated with inflammation and suggested to be involved in contractile abnormalities of cardiomyocytes.
Methods: In this study, we examined the association of the RETN SNPs in −420 and +299 in patients with idiopathic dilated cardiomyopathy (IDCM). Patients with IDCM (n = 250) and healthy controls (n = 250) were enrolled in this study. RETN genotyping was performed by using PCR-RFLP method.
Results: RETN −420C>G and +299G>A polymorphisms were significantly more prevalent in patient group vs. controls (P < 0.0001 and P = 0.0007, respectively). GG genotype at −420 and AA genotype at +299 were higher in the patient group compared with healthy controls (OR = 11.4, P < 0.0001, and OR = 2.3, P = 0.030, respectively). We found that the −420G allele increased the risk of developing IDCM in patients (P < 0.0001). Moreover, there was a significant difference between G and A alleles at RETN +299 from IDCM cases and controls (P = 0.0032). The RETN −420G and +299A haplotypes were more prevalent in the patient vs. control group (P < 0.0001).
Conclusion: The results suggest that the RETN −420C>G and +299G>A polymorphisms may have a role in the pathogenesis of IDCM.

1. Introduction

Dilated cardiomyopathy (DCM) is refer to a broad spectrum of heterogeneous myocardial disorders that are characterized by ventricular dilation and depressed myocardial contractility in the absence of abnormal loading conditions or ischemic heart disease that are sufficient to cause global systolic heart impairment (Manolio et al., 1992). More than 75 specific diseases can produce DCM phenotype. Thus, the DCM can be envisioned as the final common pathway for a myriad of cardiac disorders that either damage the heart muscles or, alternatively, disrupt the ability of the myocardium to generate force and subsequently cause chamber dilation (Richardson et al., 1996). This disorder is clinically heterogeneous, ranging differently in affected individuals with clinical presentations of severe symptoms, including heart failure, sudden death and asymptomatic individuals. Currently, myocarditis, immunological abnormalities, genetic factors, environmental factors, and persistent cardiotropic viral infections are all assumed to be causes of DCM (Maron et al., 2006; Richard et al., 2006).

DCM is also genetically heterogeneous and it seems clear that multiple genes, including "genes encoding sarcomeric proteins" are involved in the pathophysiology of cardiac muscles (Richard et al., 2006). Multiple gene variants have been identified to be associated with DCM, with variable individual prevalence ranging from <1% to 10% (Karkkainen and Peuhkurinen, 2007). World Health Organization/International Society and Federation of Cardiology Task Force classifies the dilated cardiomyopathy as idiopathic dilated cardiomyopathy (IDCM) with unknown causes and secondary dilated cardiomyopathy commonly hypertensive and ischemic cardiomyopathy (Richardson et al., 1996).

Over the past decade, much attention has been focused to identify the genetic factors that could affect the pathogenesis of IDCM, as 20% of IDCM patients were found to have a familial link (Grunig et al., 1998). Some susceptible genes, including HLA-DQA1-0501, HLA-DRB1-1401, exon 8 C/T of Endothelin receptor A, Leu10Pro of TGF-beta1, and G994T of PAF acetyl hydrolase have been shown to be associated with an increased risk of developing IDCM (Ichihara et al., 1998; Small et al., 2002). Additionally, interleukin-23 (IL-23) receptor (Chen et al., 2009), TNF-alpha (Liang et al., 2010), IL-6 and interleukin-10

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(Adamopoulos et al., 2011) have also identified and associated with the pathogenesis of IDCM. Recently, resistin, an adipocyte derived peptide has been linked with cardiac abnormalities (Kim et al., 2008; Hussain et al., 2010). Further studies on inflammatory cytokine gene polymorphism and their expression in relation to IDCM could be quite useful for better understanding of the factors affecting the disease pathology, as RETN +299G>A polymorphism has not been investigated so far.

The purpose of this study was to investigate the association of RETN −420C>G and +299G>A polymorphisms with idiopathic dilated cardiomyopathy in a Pakistani population.

2. Materials and methods

2.1. Study population

Two hundred and fifty IDCM patients with mean age of 53.5 ± 13.9 years and an equal number of healthy subjects with mean age of 52.4 ± 12.0 years were investigated in this case–control hospital based study. After obtaining the medical history, all subjects underwent physical examination, coronary angiography, two-dimensional echocardiography, and Doppler studies in the Federal Government Polyclinic Hospital, Islamabad. The clinical diagnosis of idiopathic dilated cardiomyopathy was based on the revised criteria established by the World Health Organization in 1995 (Richardson et al., 1996). The inclusion of patients was made in the presence of fractional shortening (<25%), ejection fraction (<40%), left ventricular end diastolic diameter (>70 mm), and exclusion of any known causes of dilated cardiomyopathy like diabetes, coronary artery disease, viral myocarditis, hypertension, valvular heart disease, insulin resistance and other types of cardiomyopathies. Control subjects were from same ethnic region, and were healthy with normal 12-lead ECG and echocardiography. Written informed consent was obtained from all subjects in order to use blood samples, according to the Helsinki Declaration of 1975 as revised in 1997. The study protocol was approved by the Institutional Review Board, Quaid-i-Azam University.

2.2. Sample collection and DNA isolation

Venous blood samples were collected from patients with IDCM and healthy control subjects. For serum separation, blood samples were clotted at room temperature and then centrifuged at 5000 rpm for five minutes by using Eppendorf centrifuge 5417R, Germany. Serum was stored at −80 °C for further biochemical analysis. For DNA analysis, venous blood samples were collected in ethylenediamine tetra acetic acid (EDTA) tube to prevent the coagulation of blood. Genomic DNA was isolated from venous blood samples using standard phenol-chloroform extraction method.

2.3. Biochemical analysis

Biochemical analysis of total-cholesterol, triglycerides, LDL-C and HDL-C was carried out by using AMP Diagnostic kits (Austria). Assays were performed according to manufacturing recommendation by using a Vitalab Selectra E chemistry analyzer (Netherlands) as discussed earlier (Hussain et al., 2010).

2.4. Genotyping

Polymorphisms of the RETN gene in 5′-flanking and entrance region were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method (Fig. 1). Genomic region containing −420C>G polymorphism of RETN gene was amplified by using forward primer 5′-TGT CAT TCT CAC CCA GAG AC-3′ and reverse primer 5′-TGG GCT CAG CTA ACC AAA TC-3′, as previously reported (Hussain et al., 2011). DNA segment of 173 bp of RETN intron 2 containing +299G>A polymorphism was amplified by forward primer

5′-CAG CGC TCA CCA AAT CTC ATC C-3′ and the reverse primer 5-TCC AGG ACC CTG TCT TGA GTT GG-3′. The PCR-RFLP was carried out according to an earlier study (Hussain et al., 2011).

2.5. Statistical analysis

Statistical analysis was carried out by using GraphPad Instat 3.05 (GraphPad Software Inc., San Diego, California). Comparison of continuous variables and categorical variables was performed using Yates Corrected chi-square test and Mann–Whitney test, respectively. Genotype frequencies of each −420C>G and +299G>A polymorphism between two groups were compared by chi-square test. Allele frequencies were calculated by counting total alleles divided by the total number of chromosomes. Allele frequencies were compared between patients and controls by using Fisher's exact test; odds ratio and 95% confidence intervals were given accordingly. The results were considered significant with $P < 0.05$.

3. Results

3.1. Characteristics of study population

Baseline characteristics, and clinical features of patients with IDCM and healthy controls are listed in Table 1. The patient group contained 81.6% and 18.4%, whereas the control group of healthy subjects contained 82.4% and 17.6% men and women, respectively. Tobacco smokers were 13.2%, and 11.2% in the patient group and the control group, respectively. There was no significant difference in age, gender and smoking status between patients and control subjects ($P > 0.05$; for each variable; Table 1). In addition, there was no significant difference in the levels of TC, TG, LDL-C, and HDL-C from patients with IDCM and control subjects ($P > 0.05$; Table 1). The patient group showed lower systolic blood pressure than control subjects ($P = 0.0203$; Table 1). There was no significant difference in diastolic blood pressure between patients and control subjects ($P = 0.0586$; Table 1).

3.2. Genotype analysis

The genotype distribution of −420C>G polymorphism in IDCM patients indicated a significant difference among the patients and control subjects ($P < 0.0001$; Table 2) (P value from 3×2 contingency table). Moreover, assuming a co-dominant model, at position −420 of RETN, GG genotype was more prevalent in the patient group compared with the control group (OR = 11.4, 95% CI = 5.27–24.71; $P < 0.0001$; Table 2). Under the dominant model, the combined genotype frequency of CG + GG vs. CC was significantly higher in IDCM patients compared with the control group (OR = 4.3, 95% CI = 2.68–6.98, $P < 0.0001$; Table 2). RETN −420G mutant allele was more frequent (53.2%) in patients with IDCM. There was a statistically significant difference between the C and G alleles in the IDCM patient and healthy control groups (OR = 2.09, 95% CI = 1.62–2.69, $P < 0.0001$; Table 2).

Regarding +299G>A polymorphism, genotype distribution was significantly different between patient and control groups ($P = 0.0020$; Table 2) (P value from 3×2 contingency table). GA genotype was more prevalent in the patient group compared with the control group ($P = 0.0014$, OR = 1.8, 95% CI = 1.28–2.70; Table 2). Also, carriers of the AA genotype indicated an increased risk of disease development compared with control subjects ($P = 0.030$, OR = 2.3, 95% CI = 1.01–5.18; Table 2). Moreover, combined genotype frequency of GA + AA was significantly higher in IDCM patients compared with the control group ($P = 0.0007$, OR = 1.9, 95% CI = 1.32–2.74; Table 2) (P value from GG vs. GA + AA genotypes). Subsequently, RETN +299A allele was more frequent (38.2%) in patients compared with controls (29.2%). There was a statistically significant difference between the G and A alleles in the IDCM patient and healthy control groups ($P = 0.0032$, 95% CI = 1.32–2.74; Table 2).
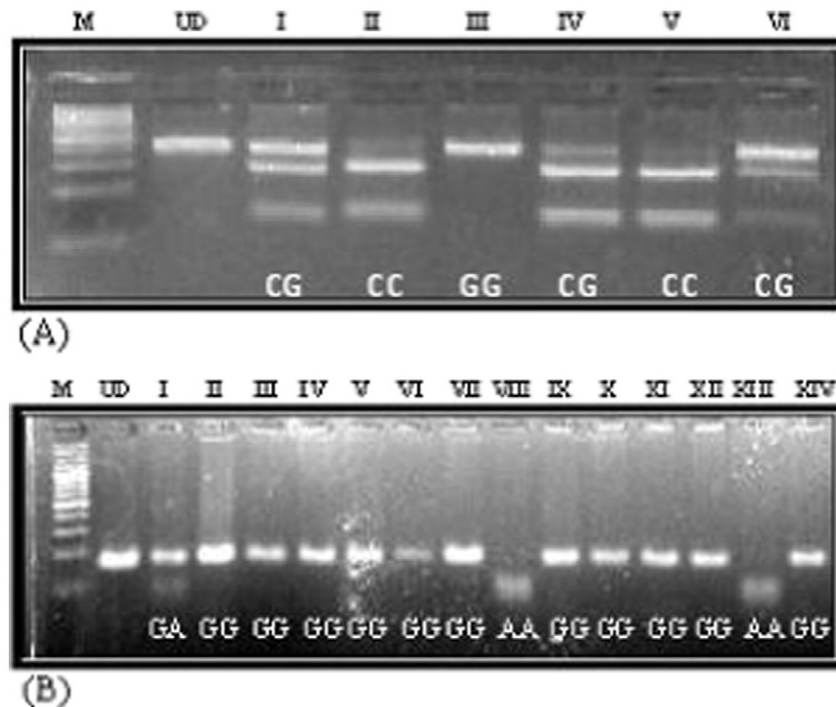
Fig. 1. Electropherogram of tedium bromide stained 3% agarose gel showing a genotype pattern of (A) BbsI restriction digest at RETN −420C/G polymorphism and (B) Alu1 restriction digest at RETN +299G/A polymorphism. The wells are identified as: M, nucleotide fragment size marker; UD, PCR product before restriction enzyme processing; I–VI and I–XIV, different genotypes after restriction reaction.

3.3. Haplotype analysis of the study population

Haplotype frequencies of two analyzed loci in patients and controls are summarized in Table 3. RETN −420G and +299A alleles-bearing haplotype was more frequent in patients (8.8%) compared with controls (4.0%). G–A haplotype was more prevalent in the patient group compared with the control group (OR = 4.9, 95% CI = 2.66–9.92, P < 0.0001; 3). C–A and G–G haplotypes were also significantly prevalent in patients as compared to healthy control subjects (P < 0.05).

4. Discussion

In cardiovascular phenotypes, a genetic factor is an important determinant of non-familial dilated cardiomyopathy. It was thought that pathogenesis of this disorder is modulated by the interaction of genetic and environmental risk factors. The response of cardiac tissue toward stimuli may be modulated by multiple genes that interact with each other,

resulting in phenotype, which is likely the outcome of the interaction of the responsible genes with the genetic background and the environment (Brugada et al., 1997). To our knowledge, this is the first hospital based case–control study to assess the correlation of two RETN gene polymorphisms with idiopathic dilated cardiomyopathy. In this study, we have detected a significant association of RETN −420C>G and +299G>A polymorphisms with the prevalence of idiopathic dilated cardiomyopathy in Pakistan.

IDCM is characterized by dilatation and impaired contraction of either left ventricle or both ventricles, which may lead to cardiac morbidity and mortality due to congestive heart failure or arrhythmias (Wolf et al., 2005). A number of genes encoding sarcomeric protein (Chang and Potter, 2005), cytoskeletal protein (Jefferies and Towbin, 2010),

Table 1
Basic and clinical characteristics of IDCM patients and control subjects.

Parameters	Patients (n = 250)	Controls (n = 250)	P value
Age (years)	53.5 ± 13.9	52.4 ± 12.0	0.1925[a]
Weight (kg)	67.8 ± 9.4	66.8 ± 9.3	0.1862[a]
Men/women (n,%)	204 (81.6)/46 (18.4)	206 (82.4)/44 (17.6)	0.9074[b]
Smoker/non-smokers (n,%)	33 (13.2)/217 (86.8)	28 (11.2)/222 (88.2)	0.5850[b]
SBP (mm Hg)	119.7 ± 10.6	122.5 ± 15.7	0.0203[a]
DBP (mm Hg)	82.5 ± 7.2	84.7 ± 14.5	0.0586[a]
TC (mg/dL)	173.9 ± 41.1	169.8 ± 47.0	0.2316[a]
TG (mg/dL)	128.5 ± 49.3	127.4 ± 54.9	0.6343[a]
LDL (mg/dL)	99.0 ± 28.3	97.2 ± 27.8	0.7975[a]
HDL (mg/dL)	37.8 ± 12.5	37.9 ± 9.3	0.3117[a]

Values are given as means ± SD.

n, number of subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a] P values were calculated by using the Mann–Whitney test.
[b] P values were calculated from the Pearson chi-square test.

Table 2
Genotype and allele distribution of RETN −420C>G and +299G>A polymorphisms in patients with IDCM and healthy control subjects.

SNP	Alleles/ genotypes	Controls (n = 250)	Patients (n = 250)	P value	OR (95% CI)
−420C/G	C	324 (64.8)	234 (46.8)	Reference	
	G	176 (35.2)	266 (53.2)	<0.0001[b]	2.09 (1.62–2.69)
	CC	86 (34.4)	27 (10.8)	Reference	
	CG	152 (60.8)	180 (72.0)	<0.0001[a]	3.7 (2.32–6.11)
	GG	12 (4.8)	43 (17.2)	<0.0001[a]	11.4 (5.27–24.71)
DM	CC	86 (34.4)	27 (10.8)	Reference	
	CG + GG	164 (65.6)	223 (89.2)	<0.0001[a]	4.3 (2.68–6.98)
+299G/A	G	354 (70.8)	309 (61.8)	Reference	
	A	146 (29.2)	191 (38.2)	0.0032[b]	1.4 (1.15–1.95)
	GG	117 (46.8)	79 (31.6)	Reference	
	GA	120 (48.0)	151 (60.4)	0.0014[a]	1.8 (1.28–2.70)
	AA	13 (5.2)	20 (8.0)	0.030[a]	2.3 (1.01–5.18)
DM	GG	117 (46.8)	79 (31.6)	Reference	
	GA + AA	133 (53.2)	171 (68.4)	0.0007[a]	1.9 (1.32–2.74)

Values are given as the number of alleles and genotypes with percentages in parenthesis.

n, number of subjects; OR, odds ratio; 95% CI, 95% confidence interval; DM, dominant model.

[a] P values were calculated by chi-square test (Pearson uncorrected).
[b] P values were calculated by Fisher's exact test.

Table 3
Haplotype distribution of RETN −420C>G and +299G>A polymorphisms in IDCM patients and control subjects.

Haplotype −420/+299	Patients (n = 250)	Controls (n = 250)	χ^2	OR (95% CI)	[a]P value
C–G	87 (17.4%)	196 (39.2%)	Reference		
C–A	147 (29.4%)	127 (25.4%)	29.0	2.6 (1.81–3.74)	<0.0001
G–G	222 (44.4%)	157 (31.4%)	39.3	3.1 (2.27–4.46)	<0.0001
G–A	44 (8.8%)	20 (4.0%)	30.4	4.9 (2.66–9.92)	<0.0001

The percentages were shown in parenthesis; n, number of subjects; χ^2, chi-square; OR, odds ratio.

[a] P value was calculated by chi-square test.

nuclear membrane protein (Parvari and Levitas, 2012), Z-disk and intercalated protein (Olson et al., 2002) are involved in the pathogenesis of DCM. Reported nucleotide variations in the investigated genes account for a small proportion of the molecular factors associated with the disease pathology. Therefore, there is a continuing effort around the world to unravel the additional genetic variants that may contribute to the development of cardiovascular disease. An association between the resistin gene polymorphism and cardiac hypertrophy in a Pakistani population was reported by our group (Hussain et al., 2010). It was of interest to investigate whether there is any possible link between the variant genotype at −420 and +299 of RETN with IDCM. Data from the study population revealed a significant association of the variant genotype at −420C>G (P < 0.0001) and +299G>A (P = 0.0007) from IDMC cases vs. controls. Haplotype frequencies of the two analyzed loci demonstrated that the −420G and +299A haplotype was more frequent in patients compared with the control group (P < 0.0001).

Evidence suggests that resistin is expressed in the rat heart cardiomyocytes and that the over expression of the cytokine in the cells affects their contraction and relaxation mechanics (Kim et al., 2008). Furthermore, it has been observed that resistin leads to deterioration of ischemia reperfusion injury in the rat hearts (Kim et al., 2008), and that the cytokine over expression by adenoviral vector in the ventricular myocytes affected AMP-activated protein kinase activity (AMPK) (Kang et al., 2011). These findings suggest that resistin may lead to the development of cardiomyopathy via AMPK and c-Jun N-terminal kinase pathways. Although, resistin gene regulation is poorly understood at present. Single nucleotide variations in the non-coding regions of DNA may influence the post-transcriptional regulation of mRNA that could affect translational efficiency (Pesole et al., 2001). Evidence shows that single nucleotide variations in the intronic region of transcription factor activate enhancer binding protein-2β that affected the transcriptional activity of the gene that confer susceptibility to type 2 diabetes (Tsukada et al., 2006). Therefore, it is reasonable to assume that the −420C>G and +299G>A substitutions may lead to the increased expression of the resistin gene in the study population, which may be associated with the pathology of IDCM.

In a case–control study from a German population, it has been observed that a polymorphism in the intron 2 of HSPB7 gene (rs1739843) is associated with the pathology of DCM (Stark et al., 2010). Cappola and colleagues have also reported a link between rs1739843 and ischemic and non-ischemic heart failure (Cappola et al., 2010). A number of studies have demonstrated that gene mutations in structural components of the cardiomyocytes lead to structural and functional complications of the heart. Variations in genes encoding HLA-DQA1-0501, HLA-DRB1-1401, exon 8 C/T of Endothelin receptor A, Leu10Pro of TGF-beta1, and G994T of PAF acetyl hydrolase have been shown to increase the susceptibility to an increased risk of DCM (Ichihara et al., 1998; Small et al., 2002). From this perspective, it is probable to assume that the RETN −420C>G and +299G>A polymorphisms may contribute to the IDCM pathophysiology in the study population. SNPs in the resistin gene may affect its expression by enhancing the RETN promoter activity as evidenced in the case of the −420G allele

(Osawa et al., 2004). The RETN variant genotypes in the study population may lead to increased concentrations of the cytokine in circulation, which may contribute to the pathogenesis of IDCM.

There are some potential limitations to the present study. Although, this the first attempt to study the association of the RETN SNPs with IDCM with a reasonable sample size, some significant associations of the polymorphism may be due to chance. In the present study, to our best effort, our controls were from the same geographical location as the patients. However, we cannot overlook the population stratification as we noted Hardy Weinberg deviation of a control population. The reason may be due to difference in the origins of the study population, variations in sample size or presence of selection pressure. Second, we did not show the possible link of RETN SNPs with clinical parameters of IDCM, therefore, we overlooked the link of RETN variants with the disease severity. More studies with larger sample size from different populations are warned to validate the novel observation of our study.

In conclusion, we demonstrate a significant association of RETN gene polymorphisms in −420 and +299 with IDCM patients. This study should be considered as an exploratory investigation demonstrating an association of the said SNPs with the disease phenotype, and not the causative factors of the disease. These findings should be replicated from larger cohorts of a Pakistani population with the disease phenotypes and in other high risk populations to establish the link of the SNPs with the disease to confirm the findings of this study.

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgments

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