Biomedical Research 2017; 28 (13): 6059-6063 *ISSN 0970-938X*
www.biomedres.info

Role of *cystathionine β synthase* gene variant in Sudanese population.

Taghreed Mohamed Osman Derar[1,2*], Abdel Galil Mohamed Abdel Gader[3], Anwaar Ahmed Yousif Kordofani[4], Sami Habiballa Abdalla[1], Imran Ali Khan[5]

[1]College of Applied Studies and Community Services, King Saud University, Riyadh, Saudi Arabia

[2]Al Neelain University, Sudan

[3]College of Medicine, King Saud University for Health Sciences, Saudi Arabia

[4]University of Khartoum, college of Medicine, Sudan

[5]Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, King Saud University, Riyadh, Saudi Arabia

Abstract

Several studies showed the relation between renal and Cardiovascular Diseases (CVD) with distinct genotypes. The current study aims to investigate the association with 844ins68 polymorphism on *Cystathionine β-synthase* (*CβS*) gene in renal and CVD with Sudanese population. In this pilot study, we have opted 150 cases from Khartoum state hospitals, Khartoum, Sudan. We have selected equally controls, renal and CVD (n=50). Peripheral blood was collected to perform the biochemical and molecular analysis. Genomic DNA was isolated to perform the polymerase chain reaction analysis. The current results showed the non-significant analysis with the combination of renal versus controls (OR-0.81 (0.31, 2.10); p=0.66) and CVD versus controls (OR-0.65 (0.26, 1.67); p=0.37). When we correlated renal samples and CVD cases with biochemical data and 844ins68, we found Vitamin B_{12}, D, TP, URCA and Folic acid, cholesterol to be associated (p<0.05). In conclusion, our results confirm the role of the negative association of 844ins68 polymorphism in the Sudanese population. It may be due to low sample number, and future studies should be performed with larger sample size with multiple *CβS* gene SNPs in the world's people.

Keywords: Renal, Cardiovascular, *CβS* gene, 844ins68.

Accepted on June 13, 2017

Introduction

Cardiovascular Disease (CVD) is leading cause of death, irrespective of race and ethnicity, and is mostly precipitated by cardio metabolic risk and Chronic Kidney Disease (CKD) or End Stage Renal Disease (ESRD) [1]. ESRD patients have high mortality risk as compared with general population. CVD is also a major cause of death in these patients, accounting for 40-50% of total mortality [2]. An earlier study has confirmed patients on chronic dialysis had an 8.8-times increased cardiovascular mortality risk as compared with the general population [3]. Genome-Wide Association Studies (GWASs) have been conducted in recent years and have identified common genetic variants associated with all the main risk factor traits for CVD [4]. *Cystathionine β-synthase* (*CβS*) is one of the key enzymes present in transsulfuration pathway, catalysing initial rate-limiting step by converting homocysteine to cystathionine [5]. Metabolism of homocysteine *via* the transsulfuration pathway is crucial as this helps in maintaining intracellular redox balance. Enzyme defects involved in transsulfuration pathway would lead to homocysteine accumulation of resulting in intracellular redox imbalance and could potentially lead to disease conditions [6]. There are several mutations and polymorphisms in the *CβS* gene, associated with its function and Homocysteine plasma concentrations [7]. The *CβS* gene reveals common genetic polymorphism consist 68bp insertion at position 844 (844ins68) [8]. This polymorphism was initially described in homocystinuria patients [9]. Inherited *CβS* deficiency is acknowledged to be the most frequent cause of homocystinuria in humans [10]. There are no studies carried out in Sudanese population, and this current study aims to investigate the association with 844ins68 polymorphism on *CβS* gene in renal and CVD with the Sudanese population.

Materials and Methods

Study design

This is a case-control study designed for the descriptive and qualitative approach in Sudanese population. All the analyses were limited to our study population. Accurately, 150 subjects were included in this study and all of them were divided into three categories as (i) 50 subjects with cardiovascular diseases (ii) 50 Subjects with Renal diseases and (iii) remaining 50 subjects are matching healthy control subjects. Complete samples were recruited from the Khartoum state hospitals, Khartoum, Sudan. Concern clinicians have confirmed the CVD and renal samples based on the design of the study. Healthy controls were collected from central blood bank of the similar hospital. Inclusion criteria for both the subjects are age restriction (18-60 y), local ethnicity and effected with CVD and renal diseases. The exclusion criteria were the lack of vitamin supplementation, the presence of any form of cancer, liver disease, primary renal disease or any collagenase diseases. A data collection form was designed for the recording of the patient's physical and routine laboratory data. Ethical approvals were granted by the Directorate of Research in Khartoum state in Sudan, and all subjects provided written informed consent. From each patient, 6 ml of blood sample was collected, and 4 ml of coagulant blood sample was used for biochemical and 2 ml for molecular analysis for DNA isolation [11].

Coagulant and anticoagulant blood analysis

Serum sample was separated from 4 ml of coagulant blood for biochemical analysis and measured the Homocysteine (HCV), vitamin-D, B_{12}, folic acid, albumin, blood urea nitrogen, creatinine, cholesterol, triglyceride, Urine Random Calcium/ Creatine Ratio (URCA) and Total Protein (TP) [12].

PCR analysis

Polymerase Chain Reaction (PCR) was performed with the designed primers for CBS (844 in s68) variants based on earlier publications [13]. The primers were redesigned based on the selected variants to confirm the nucleotide sequences. Three steps (denaturation, annealing and extension) with direct PCR method was applied for selected variants for genotyping. PCR amplification was performed with 35 cycles (95°C for 30 s, 60°C for 30 s, 72°C for 45 s) followed by the final extension step at 72°C for 5 min. The reaction volume contained 100 pmol of each primer, 6 µL of sterile water, 10 µL of the 2X master mix (included $MgCl_2$, 10X Taq buffer, 10 unit of Taq DNA polymerase) and 2 µL template DNA. The PCR product was directly separated by electrophoresis in 3.0% Agarose Gel (AGE) and visualised in UVI gel doc.

Statistical analysis

Statistical significance was examined by two-sided tests; statistical analyses were performed with SPSS version 21.0 software. Mean ± SD were used to measure the clinical characteristics between cases and controls with unpaired Student t-test. Allele frequencies were estimated by the gene counting method, and the chi-square (χ^2) test was used to identify departures from Hardy-Weinberg equilibrium. Genotype distribution of several polymorphisms was compared between patients and control subjects by the chi-square test. Yates correction was also carried out for genotype and allele frequencies.

Results

Biochemical and clinical analysis

The baseline characteristic features of control subjects with Renal and cardiovascular subjects have been described in Table 1. The mean age of the renal subjects was found to be 46.6 ± 16.94 compared with CVD, i.e., 54.18 ± 18.24. However, when compared with control subjects (31.92 ± 1.04) both the renal and CVD was identified as statistically significant and elder ($p<0.0001$). The gender differences between renal, CVD and control subjects are almost similar with height and weight ($p>0.05$), but BMI compared between the cases and controls were turned to be statistically significant ($p=0.04$ in renal and $p=0.01$ in CVD subjects). SBP was found to be positively associated in Renal subjects ($p=0.003$), whereas DBP was not associated in both the renal and CVD subjects.

The biochemical analysis such as Homocysteine (HCY), Vitamin B_{12}, folic acid, albumin, blood urea nitrogen, cholesterol, creatinine, total protein, triglycerides and URCA were performed between renal, CVD and control subjects (Table 2). When comparison was carried out between renal and control subjects HCY, B_{12}, FA, VIT-D, Alb, Bun, Crea, TP, URCA was significantly associated ($p<0.05$). The other tests such as Chol and Trig was not associated ($p>0.05$). The same tests were performed in CVD disease and compared with the similar controls performed in renal subjects and results confirmed HCY, B_{12}, FA, VIT-D, Alb, Bun, Crea, TP, URCA and Chol was significantly associated ($p<0.05$) and Trig was negatively associated ($p>0.05$).

Genotype analysis

The genotype and allele frequencies were carried out between renal, CVD compared with control subjects. HWE was found to be significant in both renal and CVD diseases. Table 2 describe the genotype association between renal cases and control subjects. The gene *CBS* (844 in s68) genotype significant association was not appeared between cases and controls (ID *vs.* II; OR-1.00 (0.00, 255.5), p=0.99, DD *vs.* ID OR-0.81 (0.31, 2.1), p=0.66). The Table 2 consist of allele frequencies calculated between renal cases and control subjects. C allele of C677T variants was found to be high in renal cases (95%); T allele in controls i.e., 6% (T *vs.* C: OR-0.82 (0.24-2.79); p=0.75). ID polymorphism alleles of both the cases and controls were found to be similar, i.e., D *vs.* I: OR-1.00 (0.00-255.5), p=0.00). The 844 in s68polymorphisms of *CBS* gene showed the negative association after performing the Yate's correction within the

genotypes (ID *vs.* II; OR-4.14 (0.15, 112); p=0.36; DD *vs.* ID; OR-0.65 (0.26, 1.67); p=0.37). The 844 in s68 polymorphism were not associated after incorporation of Yate's correction (T *vs.* C; OR-1.54 (0.53-4.52); p=0.42; G *vs.* A; OR-1.54 (0.53-4.52); p=1.00 and D *vs.* I; OR-0.83 (0.36-1.91); p=0.67). Statistical significant differences in allele frequencies were not observed with CVD cases and control subjects.

Table 1. *Clinical data between the renal and CVD cases with controls.*

	Renal (n=50)	Controls (n=50)	p value	Cardiovascular (n=50)	p value
Age (Years)	46.6 ± 16.94	31.92 ± 1.04	<0.0001	54.18 ± 18.24	<0.0001
Gender (M:F)	23:17	23:27	0	35:15:00	0.69
Weight (kg)	56.2 ± 15.86	67.98 ± 12.77	0.13	64.34 ± 10.66	0.2
Height (cm)	166.4 ± 9.32	166.8 ± 9.93	0.65	168.86 ± 6.31	0.01
BMI (kg/m^2)	20.25 ± 5.12	24.37 ± 3.81	0.04	22.44 ± 2.67	0.01
HTN (SBP)	145.66 ± 31.97	120 ± 17.37	0.003	113.86 ± 21.64	0.12
HTN (DBP)	81.32 ± 15.98	80 ± 13.24	0.19	73.1 ± 15.24	0.32
Smoking	04:46	10:40	0.76	07:43	0.41
HCY	23.78 ± 13.34	10.97 ± 3.29	<0.0001	27.30 ± 15.14	<0.0001
B12	389.43 ± 249.39	200.96 ± 92.81	<0.0001	523.57 ± 393.66	<0.0001
FA	17.09 ± 10.61	13.73 ± 4.63	<0.0001	14.76 ± 8.2	0.0001
VIT D	56.22 ± 33.64	51.10 ± 21.91	0.003	46.37 ± 30.74	0.01
ALB	33.73 ± 6.95	41.71 ± 4.41	0.001	30.31 ± 5.93	0.04
BUN	21.67 ± 6.45	3.90 ± 0.91	<0.0001	13.20 ± 11.46	<0.0001
CHOL	3.39 ± 0.98	3.82 ± 0.88	0.45	3.25 ± 1.42	0.001
CREA	886.39 ± 343.53	70.47 ± 15.50	<0.0001	127.86 ± 68.22	<0.0001
TP	71.45 ± 12.32	78.16 ± 4.83	<0.0001	77.06 ± 9.96	0.0001
TGL	1.28 ± 0.91	1.41 ± 0.69	0.05	1.19 ± 0.71	0.84
URCA	369.12 ± 167.58	253.28 ± 72.15	<0.0001	464.94 ± 156.80	<0.0001

Table 2. *Genotype analysis with renal and controls and CVD versus controls.*

Genotype	Renal (n=50)	Controls (n=50)	OR (95% CI)	P value
(844 in s68) II	00 (00)	01 (02%)	Reference	
(844 in s68) ID	12 (24%)	10 (20%)	1.00 (0.00, 255.5)	0.99
(844 in s68) DD	38 (76%)	39 (72%)	0.81 (0.31, 2.10)	0.66
(844 in s68) I	12 (0.12)	12 (0.12)	Reference	
(844 in s68) D	88 (0.88)	88 (0.88)	1.00 (0.00-255.5)	1
Genotype	**CVD (n=50)**	**Controls (n=50)**	**OR (95% CI)**	**P value**
(844 in s68) II	00 (00)	01 (02%)	Reference	
(844 in s68) ID	14 (28%)	10 (20%)	4.14 (0.15, 112)	0.36
(844 in s68) DD	36 (72%)	39 (72%)	0.65 (0.26, 1.67)	0.37
(844 in s68) I	14 (0.14)	12 (0.12)	Reference	
(844 in s68) D	86 (0.86)	88 (0.88)	0.83 (0.36-1.91)	0.67

Table 3. *Biochemical analysis with 844 ins68 polymorphism in ESRD patients.*

S. no	Biochemical variables	844 ins68 (DD=38)	844 ins68 (ID=12)	P value
1	Homocysteine	23.7 ± 13.1	23.9 ± 15.0	0.51
2	Vitamin B_{12}	407.3 ± 277.6	332.7 ± 136.7	0.01
3	Folic acid	16.9 ± 10.7	17.5 ± 11.2	0.78
4	Vitamin D	57.4 ± 37.6	52.5 ± 19.3	0.02
5	Albumin	34.0 ± 7.4	32.8 ± 5.8	0.44
6	Blood urea nitrogen	21.7 ± 6.8	21.3 ± 5.6	0.5
7	Cholesterol	3.2 ± 1.0	3.7 ± 0.9	0.73
8	Creatinine	882.7 ± 332.2	897.9 ± 406.2	0.34
9	TP	70.8 ± 13.8	73.3 ± 6.7	0.01
10	Triglyceride	1.2 ± 0.8	1.4 ± 1.0	0.3

11	URCA	365.2 ± 76.6	381.4 ± 122.0	0.03

Table 4. Biochemical analysis with 844 ins68 polymorphism in CVD patients.

S. no	Biochemical variables	844 in s68 (DD=36)	844 in s68 (ID=14)	P value
1	Homocysteine	27.0 ± 11.1	28.0 ± 14.5	0.22
2	Vitamin B_{12}	525.9 ± 400.2	517.5 ± 390.8	0.99
3	Folic acid	14.0 ± 6.1	16.6 ± 12.1	0.0006
4	Vitamin D	47.7 ± 32.3	42.8 ± 26.9	0.52
5	Albumin	29.4 ± 5.4	32.4 ± 6.7	0.31
6	Blood urea nitrogen	12.4 ± 10.8	15.1 ± 13.1	0.36
7	Cholesterol	2.9 ± 0.7	4.0 ± 2.2	0.0001
8	Creatinine	122.2 ± 59.9	142.3 ± 86.8	0.09
9	TP	75.9 ± 10.2	79.9 ± 8.8	0.61
10	Triglyceride	1.0 ± 0.6	1.6 ± 0.8	0.18
11	URCA	470.1 ± 159.5	451.6 ± 154.3	0.96

Discussion

This is a pilot study carried out in Khartoum state hospitals, Khartoum, Sudan and totally, 150 subjects were recruited. The results of this current study concluded there is no significant association in our population. CVD is known as the combination of heart cum blood vessels consist of arteries and veins which can effect with the heart attack, heart failure and stroke. Renal patients are prone to develop stroke or heart attack than they are to receive dialysis. Diabetes is a common risk factor for both renal and CVD's.

In *CβS* gene, a 68 bp insertion between base 844 and 845 (844ins68) at the junction of intron 7 and exon eight has been associated with lower post-methionine load increase in total Hcy concentrations [14]. The *CβS* 844ins68 polymorphism was firstly reported as a novel mutation in an Italian patient with classic homocystinuria due to CBS deficiency. The patient is heterozygous (I/N) for the mutation. Because the insertion (I allele) introduces a premature termination codon in the *CβS* mRNA, it is assumed that the truncated CBS protein is nonfunctional. However, a subsequent report [15] showed that individuals carrying the I allele of the mutation have normal size mRNA. Later, large quantities of studies showed that the 844ins68 was commonly distributed among humans as a polymorphism. The current study was found to be significantly associated with specific diseases [15-18] and with some of the studies concluded to be non-significant associations [6,10,19-25]. An earlier study [26] performed meta-analysis studies in Down syndrome offsprings in MTHFR and MTR gene and found to be the negative association. However, studies were found to be associated with a reduced risk of cleft palate in French and Belgian populations [27]. However, this study concludes the prominent involvement of the vitamin B_6-dependent transsulfuration pathway of homocysteine in OFC risk and the interest for evaluating vitamin B_6 status in further population studies. A 68 bp insertion in *CβS* gene (844ins68) and A2756G transition of *MS* gene has been found to be associated with low levels of plasma homocysteine in a population in the Midwestern region of the USA [28].

When we correlated renal samples with biochemical data and 844ins68, we found Vitamin B_{12}, D, TP and URCA to be associated ($p<0.05$; Table 3) and in Table 4, we have compared with CVD cases and found Folic acid and cholesterol to be associated ($p<0.05$). The strength of our study was, we selected purely Sudanese subjects to get the outcome more accurately, and we followed our inclusion and exclusion criteria. The limitations of this study were low sample size, selection of single SNP and excluded the correlation with combined renal and CVD diseases. In conclusion, our results confirm the role of the negative association of 844ins68 polymorphism in the Sudanese population. Future studies should be performed with larger sample size with multiple *CβS* gene SNPs in the global population.

Conflict of Interest

None

Acknowledgement

We are thankful to Dr. Salah Al Basha (AL Sha'ab Teaching Hospital- Khartoum, Mr. Maher AL Johani (KKUH, Riyadh) and Mr. Alyassa Jubartallah (Dr. Salma Centre for Renal Diseases, Khartoum).

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*Correspondence to

Taghreed Mohamed Osman Derar

College of Applied Studies and Community Services

King Saud University

Saudi Arabia