The Egyptian Journal of Medical Human Genetics 19 (2018) 379–383

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The Egyptian Journal of Medical Human Genetics

journal homepage: www.sciencedirect.com

Original article

Renalase gene polymorphisms (rs2576178 and rs10887800) in Egyptian hypertensive end stage renal disease patients

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ARTICLE INFO

Article history:
Received 6 January 2018
Accepted 26 February 2018
Available online 6 March 2018

Keywords:
End stage renal disease
Renalasegene polymorphism
Hemodialysis
Hypertenion

ABSTRACT

Background: The highly polymorphic gene encoding human renalase (RNLS) is a 311,000 bp gene located on chromosome 10.
Aim: This study aimed at studying the possible association of the two RNLS gene polymorphisms rs2576178 and rs10887800 with chronic kidney disease in general or specifically with hypertensive nephropathy in Egyptian end stage renal disease (ESRD) patients on maintenance hemodialysis.
Subjects and method: This case control study was conducted on two hundred and eighty one individuals, divided equally into two groups; an end stage renal disease patients on maintenance hemodialysis with/without hypertension and healthy matching individuals as a control group. Full clinical examination, Biochemical analysis and Molecular genetic testing were performed to detect single nucleotide polymorphism using restriction fraction length polymorphism (RFLP) for RNLS rs2576178 and rs1088780.
Results: The results of this study demonstrated that the risk of developing ESRD was increased among carriers of AA genotype for the rs10887800 (3.05 times) p = 0.001, OR = 3.05, CI95% (1.558–5.971) and GG genotype for the rs2576178 p = 0.047, OR = 1.949, CI95% (1.028–3.694).
Conclusion: Our study revealed that the risk of developing end stage renal diseases was increased among carriers of AA genotype for the rs10887800 polymorphism and GG genotype for the rs2576178 polymorphism.

1. Introduction

The renalase, also known as monoaminooxidase-C (MAO-C), is a flavoprotein enzyme that participates in the metabolism of circulating catecholamines [1]. It metabolizes catecholamines and catecholamine-like substances via a superoxide dependent mechanism using nicotinamide adenine dinucleotide (NADH) as a cofactor [2]. At least four isoforms of renalase enzyme protein have been identified. Two of them possess an unchanged amino acid domain (h-renalase 1), whereas the other two have shortened domains (h-renalase 2) [3].

Renalase is synthesized mainly by the kidneys and is excreted directly into the blood, where it participates in the metabolism of circulating catecholamines [4]. Renalase activity is not inhibited by known monoamineoxidase (MAO) inhibitors such as pargyline and clorgyline [4,5]. Renalase plays a direct significant role in the regulation of blood pressure thus its insufficiency predisposes to higher blood pressure values. [6,7]

Renalase levels were reported to be low in chronic kidney disease patients implicating its role in development of hypertension and associated morbidity and mortality in such patients [1–3]. The observation of a significant renalase deficiency in end stage renal disease (ESRD) patients was confirmed by experimental models of uremia in rats following nephrectomies [8]. Such a deficiency leads to impaired degradation of catecholamines, causing excessive tension of the sympathetic nervous system that is related to a high risk of cardiovascular diseases [9–11]. Therefore, renalase deficiency could represent an unknown pathophysiological mechanism that might partially explain the high rates of hypertension in ESRD patients.

Peer review under responsibility of Ain Shams University.
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https://doi.org/10.1016/j.ejmhg.2018.02.004
1110-8630/

The gene encoding human renalase (RNLS) is a 311,000 base pairs (bp) gene located on chromosome 10 (q23.33) that consists of 10 exons [1]. Being highly polymorphic, several single nucleotide polymorphisms (SNPs) of RNLS gene have been recently described. Single nucleotide polymorphisms (SNPs) rs2576178 GG and rs2296545 CC genotypes have been found to be associated with essential hypertension in Northern Han Chinese population [12]. Also rs2296545 CC was found to be associated with cardiac hypertrophy, dysfunction and ischemia in Caucasians [11]. Furthermore, the rs2576178 and rs10887800 GG allele were demonstrated to be significantly higher in hypertensive Egyptian type 2 diabetic patients compared to normotensive diabetic patients and control group [13].

A recent study suggested an association between two SNPs (rs2576178 and rs10887800) in RNLS gene and hypertension in Polish ESRD patients [14].

2. Aim

This study aimed at studying the possible association of the two RNLS gene polymorphisms rs2576178 and rs10887800 with chronic kidney disease in general or specifically with hypertensive nephropathy in Egyptian end stage renal disease (ESRD) patients on maintenance hemodialysis.

3. Subjects and methods

This type of case control study was conducted in the period from December 2015 to October 2016 on two hundred and eighty-one individuals, divided into two groups; a 141 end stage renal disease patients on maintenance hemodialysis with and without hypertension gathered from the nephrology unit of the internal medicine department of the Medical Research Institute Teaching Hospital, and 140 apparently healthy individuals of comparable age and gender serving as a control group, gathered from the outpatient clinics of the Institute. Informed consents were obtained from all individuals undergoing this study, which were approved by the local ethics committee of the Institute in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for research involving humans.

Full clinical examination was done to all participating individuals including duration of hemodialysis, history of hypertension, presence of type 2 diabetes mellitus (DM2), and use of antihypertensive medication, along with physical examination with stress on blood pressure measurement, and the calculation of mean blood pressure and pulse pressure. Hypertension was diagnosed according to the European Society of Cardiology guidelines for the management of arterial hypertension having $\geq$ 140 systolic and $\geq$90 diastolic as cutoff values. [15]. Patient was at a supine position for at least 5 min prior to blood pressure measurement. The average values of predialysis, systolic and diastolic blood pressures reported in the first 4 weeks of the study were collected and used for the analysis. Mean arterial pressure was calculated from the following standard equation: 1/3 of the systolic blood pressure plus 2/3 of the diastolic blood pressure. The hypertensive group, although receiving antihypertensive drugs were not strictly controlled.

3.1. Biochemical analysis

Following a twelve hours fasting period, whole venous blood sample was obtained from each subject and divided into two portions, one portion was collected in Potassium Ethylenediaminetetraacetic acid (K_3EDTA) coated vacutainer tubes for genomic studies, while the other portion was collected in serum vacutainer tubes, left to clot 10 min and centrifuged. The obtained serum was analyzed for glucose, creatinine, alanine aminotransferase, total cholesterol, high density lipoprotein cholesterol fraction, and triglycerides. Analyses were conducted using Olympus reagents, on the Olympus AU400 clinical chemistry analyzer (Beckman Coulter Inc, Brea CA, USA). The low density lipoprotein cholesterol fraction was calculated using Friedwald formula.

3.2. Molecular genetic testing

Genomic DNA was extracted from whole EDTA blood samples using Gene JET™ genomic DNA purification kit (Thermo Fischer Scientific, USA), according to the manufacturer's instructions. The purity and integrity of the extracted DNA were assessed using the NanoDrop™ 1000 spectrophotometer, utilizing the 260 and 280 nm filters and gel electrophoresis. Polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) was carried out according to the method described by Stec et al. [14]. Separate PCR was done for both SNPs. In a 25 μL reaction volume, 10–50 ng of genomic DNA were mixed with PCR master mix and primer sets specific for the DNA sequence to be amplified (Fermentas, Thermoscientific, USA). Details of primer sequences, cycler conditions and PCR product length (bp) are supplied in Table 1. Presence of the PCR products was ascertained using electrophoresis on a 2% agarose gel, with band staining using ethidium bromide. Next was the digsteion by the restriction enzymes step, were enzymes Msp I and Pst I (Fermentas, Thermoscientific, USA) were used to identify the rs2576178 and rs10887800 polymorphisms respectively in the RNLS gene, utilizing protocols supplied by the manufacturer. Restriction products were detected by electrophoresis on a 3% agarose gel that was visualized using a UV luminescence.

In the RNLS rs2576178 polymorphism, adenine replaced by guanine in the 5′-flanking region of the gene, so restriction products of 423 and 102 bp fragments denoted GG genotype while 525 bp denoted AA wild genotype. On the other hand, the RNLS rs10887800 polymorphism was characterized by guanine

Table 1
Primer sequences, cycler conditions and RFLP enzymes and conditions for both polymorphisms.

Renalase (RNLS) gene		
Primers	Forward (sense)	Reverse (Anti-sense)
rs2576178	5′-AGC AGA GAA GCA GCT TAA CCT-3′	5′-TTA TCT GCA AGT CAG CGT AAC-3′
rs10887800	5′-CAG GAA AGA AAG AGT TGA CAT-3′	5′-AA GTT GTT CCA GCT ACT GT-3′
Polymerase chain reaction conditions for both polymorphisms (rs2576178/ rs10887800)		
Cycle components	Time	Temperature (°C)
Initial denaturation	5 min	94
30–35 Cycles:		
Denaturation	2 min	94
Annealing	30sec	60
Extension	2 min	72
Final elongation	7 min	72
Amplicon (bp)	525	554
Restriction fragment length polymorphism (RFLP)		
	rs2576178	rs10887800
Enzyme	Msp I (SMEs)	Pst I
Concentration (U)	5 U	5 U
PCR product (μL)	10 μL	10 μL
Time(hours)–Temperature (°C)	6–10 h/37 °C	
3% agarose gel Electrophoresis		

Renalase (RNLS), Restriction fragment length polymorphism (RFLP)

replacing adenine in intron 6 of the gene, with restriction fragments of 415 and 139 bp representing the GG genotype while 554 bp represented the AA wild genotype.

3.3. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Comparisons between groups for categorical variables were assessed using Chi-square test (Monte Carlo). Mann Whitney test was used to compare two groups for abnormally distributed quantitative variables while ANOVA was used for comparing the studied groups and followed by Post Hoc test (LSD) for pairwise comparison. Kruskal Wallis test was used to compare different groups for abnormally distributed quantitative variables and followed by (Dunn's multiple comparisons test) for pairwise comparisons. Odd ratio (OR) used to calculate the ratio of the odds and 95% Confidence Interval of an event occurring in one risk group to the odds of it occurring in the non-risk group. Significance of the obtained results was judged at the 5% level.

4. Results

The present study is a case control study conducted on patients in Medical Research Institute their demographic data is presented in Tables 2 and 3. The mean age of the control group was 57.9 years which was significantly higher than both the hypertensive and normotensive ESRD groups which were 54.6 and 48.3 years respectively. The mean systolic and diastolic blood pressures in the control, hypertensive and normotensive ESRD groups were 117.5/75.6, 136.7/23.4 and 123.4/77.7 mmhg respectively. Family history of hypertension was observed among both hypertensive and normotensive ESRD. 51.7% of the hypertensive ESRD patients had a positive family history of hypertension while only 20.4% of normotensive ESRD had positive family history of hypertension.

Two RNLS gene polymorphisms [rs10887800 (intron 6) and rs2576178 (5′flanking region)] were genotyped in the 141 ESRD patients on maintenance hemodialysis (87 hypertensive and 54 normotensive) as well as in the 140 healthy control group.

The distributions of rs2576178 and rs10887800 gene polymorphisms genotypes in ESRD patients with or without hypertension were compared to those in the control group. The frequencies of genotypes in each group were in accordance with the Hardy Weinberg equilibrium.

As regards the rs2576178 polymorphism, significant differences in genotype distributions were observed in ESRD patients with or without hypertension when compared to those in the control group. The frequency of the wild genotype (AA) was significantly higher among healthy controls (48.6%) when compared to ESRD patients whether hypertensive or normotensive (29.1%) (P = 0.001, OR: 0.434, CI 95%: 0.265–0.710), However, The frequency of the genotype (GG) was higher among ESRD patients whether hypertensive or normotensive (28.4%) when compared to healthy controls (17.1%) (P = 0.032, OR: 1.91, CI 95%:1.080–3.392).

As for the rs10887800 polymorphism, the frequency of AA genotype was significantly higher in all ESRD patients (hypertensive and normotensive) (27.7%) compared to healthy controls (12.9%). (P = 0.003, OR: 2.592, CI 95%: 1.398–4.804) (Table 4)

When comparing polymorphism frequencies for rs2576178 between hypertensive ESRD patients (n = 87) and healthy controls (n = 140), the frequency of the AA genotype was significantly increased (p = 0.001) in healthy controls (48.6%) when compared to hypertensive renal patients (26.4%). The risk of developing ESRD induced hypertension in such patients decreased significantly with AA genotype carriers (OR = 0.381, 95%CI = 0.213–0.680).

As regards the rs10887800 the frequency of AA genotype was significantly higher (p = 0.001) in hypertensive renal patients (31.0%) compared to healthy controls (12.9%), with a higher risk of develop-

Table 2
Demographic Data among different studied groups.

	Control (n = 140)	Patients		Test of Sig.	p
		With Hypertensive (n = 87)	Without Hypertensive (n = 54)		
Age					
Mean ± SD.	57.9 ± 9.6	54.6 ± 13.8	48.3 ± 14.8	F = 12.322*	<0.001*
MAP					
Mean ± SD.	89.7 ± 4.2	101.2 ± 13.8	92.9 ± 10.1	F = 40.552*	<0.001*
Systolic blood pressure					
Mean ± SD.	117.5 ± 7	136.7 ± 23.4	123.4 ± 16.3	F = 40.830*	<0.001*
Diastolic blood pressure					
Mean ± SD.	75.9 ± 4.1	82.8 ± 9.6	77.7 ± 7.9	F = 26.935*	<0.001*
Pulse pressure					
Median (Min. – Max.)	40 (25–55)	50 (30–110)	40 (30–90)		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the three groups
F, p: F and p values for **ANOVA test**, Significance between groups was done using **Post Hoc Test (LSD)**
H, p: H and p values for **Kruskal Wallis test**, Significance between groups was done using **Post Hoc Test (Dunn's multiple comparisons test)**
*: Statistically significant at $p \leq 0.05$

Table 3
Comparison between the two studied groups according to family history of hypertension and duration of dialysis.

	Patients		Test of Sig.	p
	With Hypertensive (n = 87)	Without Hypertensive (n = 54)		
Family history of HTN				
No	42 (48.3%)	43 (79.6%)	χ^2 = 13.681*	<0.001*
Yes	45 (51.7%)	11 (20.4%)		
Duration of dialysis				
Median (Min. – Max.)	5 (0–20)	5 (1–26)	U = 2274.0	0.749

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups
U, p: U and p values for **Mann Whitney test** for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

Table 4
The distributions of rs2576178 and rs10887800 gene polymorphisms genotypes in ESRD patients with or without hypertension were compared to those in the control group.

Groups/SNP		Control (1) n = 140 /280 Frequency (%)	Patients (2) n = 141/282 Frequency (%)	P - Value	OR	CI 95%
S178	Allele A	184 65.7%	142 50.4%	0.0002*	0.5292	0.3768–0.7433
	Allele G	96 34.3%	140 49.6%	0.0002*	1.8897	1.3454–2.6541
	AA	68 48.6%	41 29.1%	0.001*	0.434	0.265–0.710
	GA	48 34.3%	60 42.6%	0.178	1.420	0.876–2.301
	GG	24 17.1%	40 28.4%	0.032*	1.914	1.080–3.392
S800	Allele A	113 40.4%	150 53.2%	0.002*	1.6794	1.2023–2.3459
	Allele G	167 59.6%	132 46.8%	0.002*	0.5954	0.4263–0.8318
	AA	18 12.9%	39 27.7%	0.003*	2.592	1.398–4.804
	AG	77 55.0%	72 51.1%	0.551	0.854	0.534–1.365
	GG	45 32.1%	30 21.3%	0.044*	0.571	0.333–0.976

ESRD = end stage renal disease, SNP = single nucleotide gene polymorphism, n = number, OR = odds ratio, CI = confidence interval, P- Value = p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Table 5
The distributions of rs2576178 and rs10887800 gene polymorphisms between hypertensive ESRD patients and the control group.

Groups/SNP		Control (1) n = 140 Frequency (%)	Patients (2) n = 87 Frequency (%)	P - Value	OR	CI 95%
S178	Allele A	184 65.7%	85 48.9%	0.0004*	0.4983	0.3386–0.7333
	Allele G	96 34.3%	89 51.1%	0.0004*	2.0069	1.3638–2.9533
	AA	68 48.6%	23 26.4%	0.001*	0.381	0.213–0.680
	GA	48 34.3%	39 44.8%	0.124	1.557	0.900–2.694
	GG	24 17.1%	25 28.7%	0.047*	1.949	1.028–3.694
S800	Allele A	113 40.4%	98 56.3%	0.001*	1.9057x	1.2992–2.7952
	Allele G	167 59.6%	76 43.7%	0.001*	0.5247x	0.3578–0.7697
	AA	18 12.9%	27 31.0%	0.001*	3.050	1.558–5.971
	AG	77 55.0%	44 50.6%	0.585	0.837	0.490–1.431
	GG	45 32.1%	16 18.4%	0.031*	0.476	0.249–0.910

ESRD = end stage renal disease, SNP = single nucleotide gene polymorphism, n = number, OR = odds ratio, CI = confidence interval, P- Value = p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

ing ESRD induced hypertension (OR = 3.050, 95%CI = 1.558–5.971). However, no significant differences in the genotype frequencies for RNLS gene rs2576178 and rs2576800 polymorphisms were noted when comparing polymorphism frequencies for non-hypertensive renal patients and healthy controls. (Tables 5 and 6)

When comparing polymorphism frequencies in both rs2576178 and rs10887800 between hypertensive and normotensive ESRD patients, no statistically significant differences were noted in the AA, AG and GG genotypes in both polymorphisms. (Table 7)

5. Discussion

The risk of developing high blood pressure is greater in patients suffering from ESRD particularly those on maintenance HD due to many contributing factors mainly hypervolemia and increased sympathetic activity. Great focus has been recently directed towards the genetic factor as a main contributor to hypertension especially in this population.

Renalase has been the focus of many studies identifying its role in blood pressure regulation and susceptibility to diseases[6][7]. In the present case–control study, the possibility of an association between two SNPs (rs2576178 and rs10887800) in RNLS gene and hypertension in Egyptian ESRD patients on maintenance hemodialysis was evaluated.

The genotypes of RNLS gene rs2576178 and rs10887800 polymorphisms were analyzed in hypertensive and normotensive ESRD patients on maintenance hemodialysis as well as in a control group of healthy individuals in order to find out the possible association

Table 6
The distributions of rs2576178 and rs10887800 gene polymorphisms between non hypertensive ESRD patients and the control group.

Groups/SNP		Control (1) n = 140 Frequency (%)	Patients (2) n = 54 Frequency (%)	P - Value	OR	CI 95%
S178	Allele A	184 65.7%	57 52.8%	0.019*	0.5831	0.3714–0.9156
	Allele G	96 34.3%	51 47.2%	0.019*	1.7149	1.0921–2.6929
	AA	68 48.6%	18 33.3%	0.056	0.529	0.275–1.020
	GA	48 34.3%	21 38.9%	0.548	1.220	0.637–2.334
	GG	24 17.1%	15 27.8%	0.098	1.859	0.887–3.897
S800	Allele A	113 40.4%	52 48.2%	0.17	1.3723	0.878–2.145
	Allele G	167 59.6%	56 51.8%	0.17	0.7287	0.4662–1.139
	AA	18 12.9%	12 22.2%	0.106	1.937	0.861–4.354
	AG	77 55.0%	28 51.9%	0.693	0.881	0.470–1.653
	GG	45 32.1%	14 25.9%	0.399	0.739	0.365–1.495

ESRD = end stage renal disease, SNP = single nucleotide gene polymorphism, n = number, OR = odds ratio, CI = confidence interval, P- Value = p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Table 7
The distributions of rs2576178 and rs10887800 gene polymorphisms between hypertensive and normotensive ESRD patients.

Groups/SNP		Hypertensive Patients n = 87 Frequency (%)	Normotensive ESRD patients n = 54 Frequency (%)	P - Value	OR	CI 95%
S178	Allele A	85 48.9%	57 52.8%	0.542	0.855	0.5284–1.382
	Allele G	89 51.1%	51 47.2%	0.542	1.1702	0.7236–1.825
	AA	23 26.4%	18 33.3%	0.381	1.391	0.664–2.915
	GA	39 44.8%	21 38.9%	0.488	0.783	0.392–1.564
	GG	25 28.7%	15 27.8%	0.902	0.954	0.448–2.030
S800	Allele A	98 56.3%	52 48.2%	0.219	1.3887	0. 8577–2.2484
	Allele G	76 43.7%	56 51.8%	0.219	0.7201	0.4448–1.166
	AA	27 31.0%	12 22.2%	0.255	0.635	0.289–1.393
	AG	44 50.6%	28 51.9%	0.883	1.052	0.534–2.076
	GG	16 18.4%	14 25.9%	0.288	1.553	0.687–3.510

ESRD = end stage renal disease, SNP = single nucleotide gene polymorphism, n = number, OR = odds ratio, CI = confidence interval, P- Value = p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

between RNLS gene rs2576178 and rs10887800 polymorphisms and hypertensive ESRD.

Based on literature review [16],[17]] regarding the link between these two polymorphisms and the risk of developing hypertension, controversial findings were observed. A study done by Zhao et al. [16] on Northern Han Chinese population reported the association of RNLS gene rs2576178 polymorphism with essential hypertension [16]. Stec et al. confirmed the same finding by revealing an increased risk of hypertension in Polish Caucasian ESRD hypertensive patients who were carriers of G allele in both rs2576178 and rs10887800 RNLS gene polymorphisms, it has to be noted that healthy volunteers were not examined in that study.[14]. However Abdallah et al. [17], reported no statistically significant difference in G allele frequency between hypertensive and normotensive ESRD patients, as well as the absence of a significant increase in the risk of developing hypertension in G allele carriers for both rs2576178 and rs10887800 RNLS gene SNPs. These findings were confirmed by Kiseljakovic et al. [18], who confirmed no significant association between RNLS gene rs2576178 polymorphism and hypertension in HD patients. Our study confirmed the findings of both Abdallah et al. [17] and Kiseljakovic et al. [18] where no significant association was found between RNLS gene rs2576178 and/or rs10887800 polymorphisms and hypertension among hypertensive HD cases in a cohort of Egyptian population.

As regards the rs2576178, our results demonstrated a protective effect for AA carriers against risk of developing ESRD. On the contrary Kiseljakovic et al. found no association of this RNLS gene polymorphism and renal function in population of Bosnia and Herzegovina [18].

On the other hand, the results of this study demonstrated that the risk of developing ESRD was increased among carriers of AA genotype for the rs10887800 (3.05 times) p = 0.001, OR = 3.05, CI 95% (1.558–5.971) and GG genotype for the rs2576178 p = 0.047, OR = 1.949, CI 95% (1.028–3.694). Abdallah et al. found that carriers of the G allele for both polymorphisms were at higher risk of developing ESRD. (18) Such an opposition can be explained that our study included larger sample size for control group (140 healthy volunteers) compared to the control group in the study done by Abdallah et al. (50 healthy volunteers).

To conclude our study supports that the two studied polymorphisms rs2576178 and rs10887800 in the RNLS gene *a*re not associated with increased risk of developing hypertension among Egyptian end stage renal disease patients. However, our study revealed that the risk of developing end stage renal diseases was increased among carriers of AA genotype for the rs10887800 polymorphism and GG genotype for the rs2576178 polymorphism. We recommend that further studies should be conducted to investigate this association on a larger sample size to confirm our findings.

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