IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2012; 9(4):274-279. doi: 10.7150/ijms.4171

Research Paper

Pooled Analyses of the Associations of Polymorphisms in the *GRK4* and *EMILIN1* Genes with Hypertension Risk

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Received: 2012.01.31; Accepted: 2012.05.14; Published: 2012.05.24

Abstract

Background: The *GRK4* and *EMILIN1* genes have been suggested to be involved in the development of hypertension. However, the results have been inconsistent. In this study, a meta-analysis was performed to clarify the associations of polymorphisms in the *GRK4* and *EMILIN1* genes with hypertension risk.

Methods: Published literature from PubMed and Embase databases were retrieved. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed- or random-effects model.

Results: Five studies for polymorphisms in the *GRK4* gene and five studies for polymorphisms in the *EMILIN1* gene were identified. The results suggested that rs1801058 polymorphism in the *GRK4* gene was inversely associated with hypertension among East Asians (TT vs. CC: OR=0.39, 95%CI 0.28-0.55) and positively associated with hypertension among Europeans (TT vs. CC: OR= 2.38, 95%CI 1.38-4.10). Rs2960306 polymorphism in the *GRK4* gene was significantly associated with hypertension among Europeans (TT vs. GG: OR=1.92, 95%CI 1.13-3.27). The significant associations were also observed for rs2011616 and rs2304682 polymorphisms in the *EMILIN1* gene among Japanese (rs2011616: AA vs. GG: OR=0.38, 95%CI 0.18-0.82; rs2304682: GG vs. CC: OR=0.37, 95%CI 0.17-0.81) but not among Chinese.

Conclusions: This meta-analysis suggested that rs1801058 polymorphism in the *GRK4* gene was associated with hypertension in East Asians and Europeans. The significant association was also found for rs2960306 polymorphism in the *GRK4* gene among Europeans. In addition, there were significant associations of rs2011616 and rs2304682 polymorphisms in the *EMILIN1* gene with hypertension among Japanese.

Key words: Hypertension, GRK4, EMILIN1, Polymorphism, Meta-analysis.

Introduction

Hypertension is associated with stroke and cardiovascular disease which are major causes of global health burden [1]. Epidemiological studies have suggested that environmental factors (e.g. excess alcohol consumption, increased salt intake, and less physical activity) could increase the risk of hypertension [2]. However, many studies supported that hypertension is a complex disease resulting from the interactions of genes and environmental factors [3]. Twin studies have shown that approximately 50% of blood pres-

sure variation was determined by genetics [4]. Therefore, the identification of new susceptibility genes would help further elucidate the underlying molecular mechanisms of hypertension.

G protein-coupled receptor kinase 4 (GRK4) has been involved in the development of hypertension since it plays an important role in the desensitization of the dopamine receptor 1(D1) [5]. Dopamine contributes to sodium balance by facilitating natriuresis through activation of D1 on the renal proximal tubules [6]. Therefore, polymorphisms in the *GRK4* gene might contribute to sodium retention and hypertension through inactivation of the D1 receptor. A486V (rs1801058), R65L (rs2960306) and A142V (rs1024323) polymorphisms were the most frequently studied ones. However, the results have been inconsistent.

The elastin microfibril interfacer-1(EMILIN1) is implicated in stabilise elastin and related microfibrils, and affects vessel compliance and the blood pressure (BP). Evidences have suggested that EMILIN1 inhibits TGF-β signaling by specifically binding to the proTGF-β precursor and plays a key role in BP homeostasis [7]. To date, three polymorphisms (rs2011616, rs2304682 and rs3754734) in the *EMILIN1* gene have been reported to be associated with BP or hypertension in different ethnic populations. However, the results also have been conflicting.

Therefore, in this study, we performed the meta-analysis to clarify the associations of polymorphisms in the *GRK4* and *EMILIN1* genes with hypertension risk across different ethnic populations.

Materials and methods

Literature and search strategy

We searched the literature databases including PubMed and Embase. The search strategy to identify all possible studies involved the use of the following key words: (G-protein coupled receptor Kinase-4 or GRK4 or the elastin microfibril interfacer-1 or EMILIN1) and (variant or variation or polymorphism) and hypertension. All related studies published in English and Chinese languages were included. The reference lists of retrieved articles were hand-searched. If more than one article were published using the same data, only the study with largest sample size was included. The literature search was updated on September 13, 2011.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluated the association of polymorphism in the *GRK4* or *EMILIN1* gene with hypertension; (2) used case-control or cohort design; (3) provided sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country; (4) gender frequency and mean age of subjects in hypertensive cases and controls; (5) sample size of cases and controls; (6) genotype distribution in cases and controls; and (7) *P* value for Hardy–Weinberg equilibrium (HWE) test in controls. The two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision.

Statistical analysis

The associations of polymorphisms in the *GRK4* or *EMILIN1* gene with hypertension were estimated by calculating pooled ORs and 95% CIs under a co-dominant, a dominant and a recessive genetic model, respectively. The significance of pooled OR was determined by *Z* test ($p<0.05$ was considered statistically significant). Q test was performed to evaluate to the between-study heterogeneity. A random- (DerSimonian-Laird method [8]) or fixed- (Mantel-Haenszel method [9]) effects model was used to calculate pooled OR in the presence ($p<=0.10$) or absence ($p>0.10$) of heterogeneity, respectively. Subgroup analysis by ethnicity was performed. Begg's funnel plot, a scatter plot of effect against a measure of study size, was generated as a visual aid to detect bias or systematic heterogeneity [10]. Publication bias was assessed by Egger's test [11] ($p<0.05$ was considered statistically significant). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA). To correct for multiple comparisons, the false discovery rate (FDR) approach was used [12]. FDR analysis (0.05 as criteria) was applied for four genetic models, six polymorphisms, 12 groups for three polymorphisms in the *GRK4* gene and 7 groups for three polymorphisms in *EMILIN1* gene simultaneously (number of tests: $4\times4\times3+4\times7=76$).

Results

Characteristics of the studies

The literature search identified a total of 41 potentially relevant papers. Of these, 27 papers were excluded because of obvious irrelevance by reading the titles and abstracts. In addition, three reviews [13-15], one duplicated publication [16], and one paper [17] which assessed the associations of polymorphisms with salt-sensitive hypertension was excluded. It should be noted that the paper by Shen et al. [23]

contained two studies. Finally, five studies for polymorphisms in the *GRK4* gene [18-22] and five studies for polymorphisms in the *EMILIN1* gene [23-26] met the inclusion criteria and were included in the meta-analysis. The characteristics of the included studies were listed in Table 1.

Meta-analysis results

Regarding *GRK4* gene, five studies (1000 cases and 1059 controls) for rs1801058 polymorphism, five studies (1012 cases and 1119 controls) for rs2960306 polymorphism, and five studies (1018 cases and 1004 controls) for rs1024323 polymorphism were included in the meta-analysis. The results indicated no significant association for all three polymorphisms with the risk of hypertension under all genetic models (Table 2). Further subgroup analysis by ethnicity showed that rs1801058 polymorphism was inversely associated with hypertension among East Asians (Chinese) (TT vs. CC: OR=0.39, 95%CI 0.28-0.55; CT vs. CC: OR=0.55, 95%CI 0.40-0.75; TT+CT vs. CC: OR=0.48, 95%CI 0.36-0.64; TT vs. CT+CC: OR=0.57, 95%CI 0.43-0.76), but positively associated with hypertension among Europeans (TT vs. CC: OR= 2.38, 95%CI 1.38-4.10; CT vs. CC: OR=1.66, 95%CI 1.08-2.55; TT+CT vs. CC: OR=1.82, 95%CI 1.21-2.74; TT vs. CT+CC: OR=1.70, 95%CI 1.07-2.70). Rs2960306 polymorphism was significantly associated with hypertension among Europeans (TT vs. GG: OR=1.92, 95%CI 1.13-3.27; TT vs. GT+GG: OR=1.94, 95%CI 1.19-3.18) (Table 2).

Table 1. Characteristics of the studies included in the meta-analysis.

Study	Country	Ethnicity	Gender (M/F)		Age, mean±SD, years		Sample Size		Polymorphisms	Definitions (SBP/DBP, mmHg)	
			Cases	Controls	Cases	Controls	Cases	Controls		Hypertension	Controls
GRK4 gene											
Bengra, 2002	Italy	European	NA	NA	NA	NA	60	60	rs2960306; rsl024323; rs1801058	≥140/90	<140/90
Williams, 2004	Ghana	African	NA	NA	NA	NA	126	51	rs2960306; rsl024323; rs1801058	≥160/95 [a]	<140/90
Speirs, 2004	Australia and UK	European	67/101	178/134	54±12	47±11	168	312	rs2960306; rsl024323; rs1801058	≥140/90	<130/90
Wang, 2006	China	East Asian	262/241	257/233	53.6±9.3	53.5±9.2	503	490	rs2960306; rsl024323; rs1801058	≥160/100	<140/90
Martinez Cantarin,2010	US	African	100/73	109/130	40±6	36±8	173	239	rs2960306; rsl024323; rs1801058	≥140/90 [b]	<130/80
EMILIN1 gene											
Shen,2009	China	East Asian	262/241	257/233	53.6 ± 9.3	53.5 ± 9.2	503	490	rs2011616; rs2304682; rs3754734	≥160/100 [b]	<140/90
Shen,2009	China	East Asian	393/421	401/378	54.5 ± 10.7	53.5 ± 9.7	814	779	rs2011616; rs3754734	≥160/100 [b]	<140/90
Shimodaira,2010	Japan	East Asian	193/94	157/96	49.8 ± 6.8	51.1 ± 9.9	287	253	rs2011616; rs2304682	≥160/100	<130/85
Oh,2011	Singapore	East Asian	268/199	157/318	49.4±11.9	47.3±8.7	467	475	rs2011616	≥140/90 [c]	<134/84
Mi,2011	China	East Asian	NA	NA	52.5±9.4	49.0±10.3	201	202	rs2011616; rs2304682; rs3754734	≥140/90	<140/90

NA, not available.

[a] or who had been previously diagnosed as hypertensive.

[b] or currently taking antihypertensive medications.

[c] or mean 24-h ambulatory blood pressure ≥135/85mmHg.

Table 2. Pooled ORs and 95%CIs of the associations between polymorphisms in the *GRK4* gene and hypertension risk.

Contrasts	No. of studies (cases/ controls)	Homogeneous co-dominant model			Heterogeneous co-dominant model			Dominant model			Recessive model		
		OR	95% CI	P_H	OR	95% CI	P_H	OR	95% CI	P_H	OR	95% CI	P_H
rs1801058													
All	5 (1000/1059)	1.26	0.42-3.80	0.000	0.95	0.57-1.58	0.001	1.01	0.54-1.86	0.000	1.15	0.56-2.35	0.002
European	2 (205/308)	2.38	1.38-4.10	0.624	1.66	1.08-2.55	0.759	1.82	1.21-2.74	0.636	1.70	1.07-2.70	0.629
African	2 (292/261)	1.06	0.32-3.48	0.282	0.69	0.46-1.04	0.354	0.72	0.49-1.07	0.195	1.06	0.35-3.83	0.317
East Asian (Chinese)	1 (503/490)	0.39	0.28-0.55	-	0.55	0.40-0.75	-	0.48	0.36-0.64	-	0.57	0.43-0.76	-
rs2960306													
All	5 (1012/1119)	1.22	0.86-1.73	0.239	0.91	0.74-1.11	0.955	0.94	0.77-1.15	0.688	1.23	0.90-1.68	0.178
European	2 (220/372)	1.92	1.13-3.27	0.795	0.98	0.68-1.41	0.792	1.13	0.80-1.60	0.650	1.94	1.19-3.18	0.863
African	2 (289/257)	0.95	0.56-1.60	0.666	0.97	0.64-1.45	0.944	0.96	0.65-1.41	0.907	0.96	0.61-1.50	0.572
East Asian (Chinese)	1 (503/490)	0.62	0.22-1.76	-	0.83	0.61-1.13	-	0.81	0.60-1.10	-	0.65	0.23-1.83	-
rs1024323													
All	5 (1018/1004)	0.98	0.70-1.36	0.185	0.92	0.75-1.13	0.487	0.91	0.75-1.11	0.292	0.99	0.75-1.29	0.376
European	2 (228/249)	1.50	0.84-2.66	0.856	1.09	0.74-1.61	0.606	1.17	0.81-1.69	0.771	1.43	0.84-2.43	0.692
African	2 (287/265)	0.98	0.57-1.68	0.227	1.00	0.60-1.66	0.191	0.99	0.60-1.61	0.179	0.98	0.68-1.40	0.751
East Asian (Chinese)	1 (503/490)	0.57	0.30-1.10	-	0.82	0.63-1.08	-	0.79	0.61-1.03	-	0.61	0.32-1.16	-

P_H, P value for heterogeneity based on Q test.

Table 3. Pooled ORs and 95%CIs of the associations between polymorphisms in the *EMILIN1* gene and hypertension risk.

Contrasts	No. of studies (cases/controls)	Homogeneous co-dominant model			Heterogeneous co-dominant model			Dominant model			Recessive model		
		OR	95% CI	P_H	OR	95% CI	P_H	OR	95% CI	P_H			
rs2011616													
All	5 (2262/2189)	0.89	0.70-1.12	0.105	0.89	0.70-1.12	0.015	0.88	0.69-1.12	0.006	0.92	0.74-1.16	0.258
Chinese	4 (1975/1936)	0.97	0.76-1.24	0.478	0.94	0.73-1.21	0.020	0.95	0.75-1.21	0.020	1.00	0.79-1.27	0.777
Japanese	1 (287/253)	0.38	0.18-0.82	-	0.67	0.46-0.97	-	0.61	0.43-0.87	-	0.44	0.21-0.93	-
rs2304682													
All	3 (991/945)	1.05	0.39-2.81	0.001	1.06	0.68-1.67	0.006	1.06	0.62-1.81	0.000	1.00	0.45-2.22	0.010
Chinese	2 (704/692)	1.66	0.64-4.34	0.032	1.24	0.99-1.55	0.124	1.37	0.86-2.17	0.047	1.42	0.66-3.05	0.075
Japanese	1 (287/253)	0.37	0.17-0.81	-	0.67	0.46-0.97	-	0.61	0.43-0.87	-	0.42	0.19-0.92	-
rs3754734													
All (Chinese)	3 (1485/1468)	1.09	0.86-1.39	0.485	1.21	0.83-1.77	0.006	1.19	0.84-1.68	0.009	0.99	0.79-1.25	0.970

P_H, P value for heterogeneity based on Q test.

Regarding *EMILIN1* gene, five studies (2262 cases and 2189 controls) for rs2011616 polymorphism, three studies (991 cases and 945 controls) for rs2304682 polymorphism, and three studies (1485 cases and 1468 controls) for rs3754734 polymorphism were included in the meta-analysis. Overall, there was no significant association between three polymorphisms and hypertension among East Asians (Table 3). In the stratified analysis, the significant association was observed for rs2011616 and rs2304682 among Japanese (rs2011616 AA vs. GG: OR=0.38, 95%CI 0.18-0.82; GA vs. GG: OR=0.67, 95%CI 0.46-0.97; AA+GA vs. GG: OR=0.61, 95%CI 0.43-0.87; AA vs. GA+GG: OR=0.44, 95%CI 0.21-0.93. rs2304682 GG vs. CC: OR=0.37, 95%CI 0.17-0.81; CG vs. CC: OR=0.67, 95CI 0.46-0.97; CG+GG vs. CC: OR=0.61, 95%CI 0.43-0.87; GG vs. CG+CC: OR=0.42, 95%CI 0.19-0.92) but not among Chinese (Table 3).

The significant associations for the polymorphisms above remained even after FDR was applied, although they disappeared in some genetic models of the polymorphisms.

Discussion

To our knowledge, this is the first meta-analysis which comprehensively assessed the associations of

polymorphisms in the *GRK4* and *EMILIN1*genes with hypertension risk. To date, several studies have investigated the associations among different ethnic populations. However, the findings have been conflicting, with results of increased, decreased, or no risk of hypertension for the same polymorphism. The discrepant results might be due to many reasons such as the differences in statistical power, recruitment procedures of the study population, and the genetic and environmental backgrounds. The present meta-analysis indicated that rs1801058 polymorphism in the *GRK4* gene was inversely associated with hypertension among East Asians, but positively associated with hypertension among Europeans. In addition, there was a significant association between rs2960306 in the *GRK4* gene and hypertension among Europeans. We also observed significant associations of rs2011616 and rs2304682 polymorphisms in the *EMILIN1* gene with hypertension among Japanese.

It is possible that the effect sizes of genetic factors predisposing to human diseases are different across various ethnic populations [27]. Indeed, the distributions of most polymorphisms are much different in the various ethnic populations. Taking rs1801058 polymorphism in the *GRK4* gene for an example, the frequency of T allele is about 0.398 in European population; while it is about 0.494 in Chinese, 0.529 in Japanese, and 0.097 in African (HapMap data). Moreover, the exposure to environmental factors might be also different across different ethnic populations. Therefore, the subgroup analysis based on ethnicity was performed. The results suggested this polymorphism was inversely associated with hypertension in East Asians, but positively associated with hypertension in Europeans. However, no statistically significant association was observed in Africans. The effect of ethnic differences was also demonstrated for rs2960306 polymorphism, with the significant association only in Europeans. However, the effect of rs2011616 and rs2304682 polymorphisms in the *EMILIN1*gene on hypertension among Japanese could not be explained by ethnic differences since the genetic backgrounds are very similar between Chinese and Japanese populations. Therefore, it is possible that the effect differences were due to different environmental backgrounds or gene-environment interactions.

The mechanisms of how the rs1801058 and rs2960306 polymorphisms in the *GRK4* gene and rs2011616 and rs2304682 polymorphisms in the *EMILIN1* gene influence hypertension susceptibility among East Asians or Europeans are still unclear. GRK4 is expressed in the nephron segments of the kidney, where sodium transport is regulated by dopamine and angiotensin II [28]. The 4p16.3, where the *GRK4* gene located, has been indicated to be important in the development of hypertension [29]. Other genes, such as the α-adducin and D5 receptor genes, which close to 4p arm, have also been linked to hypertension. Those three polymorphisms in the *GRK4* gene are associated with a constitutive increase in kinase activity in proximal tubule cells from humans with essential hypertension [30]. Increases in BP, peripheral vascular resistance and reduces in vessel size have been observed among EMILIN1 knockout animals [7]. It has been shown that EMILIN1 links TGF-β maturation to BP homeostasis. In addition, EMILIN1 could bind specially to the proTGF-β precursor and prevent its maturation by furin convertases in the extracellular space, thereby inhibiting TGF-β signaling [7].

The current meta-analysis has some advantages compared to other individual studies; however, it does have some limitations. First, the meta-analysis was based primarily on unadjusted ORs and CIs because of the unavailability of adjusted estimates from the primary publications, and then the confounding factors might influence the precision of effect estimates. Second, the effects of gene-gene/ gene-environment interactions were not addressed in this meta-analysis. Third, the statistical power was limited in the subgroup analysis based on ethnicity. Therefore, the conclusions should be interpreted with caution. Fourth, more than one polymorphism in *GRK4 or EMILIN1*gene was investigated among each study; however, the haplotype analysis was not performed among most studies, which impeded us for the further meta-analysis.

In summary, this meta-analysis suggested that rs1801058 polymorphism in the *GRK4* gene was associated with hypertension in East Asians and Europeans; rs2960306 polymorphism in the *GRK4* gene was significantly associated with hypertension among Europeans. In addition, there was a significant association of rs2011616 and rs2304682 polymorphisms in the *EMILIN1*gene with hypertension among Japanese. However, further studies are needed to investigate the role of polymorphisms in the *GRK4* and *EMILIN1* genes in the pathogenesis of hypertension.

Potential publication bias

No publication bias was detected for all six polymorphisms by Egger's test (all $P>0.05$).

Acknowledgements

This study was supported by Independent Innovation Foundation of Shandong University (2010GN046) and the Foundation for Outstanding

Young Scientist in Shandong Province (BS2011YY026).

Competing Interests

The authors have declared that no competing interest exists.

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