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Associations between angiotensinogen M235T polymorphisms and the risk of diabetic nephropathy: A meta-analysis

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ABSTRACT

Aims: The aim of the present study was to clarify the potential relationship of angiotensinogen (AGT) M235T polymorphism and diabetic nephropathy (DN) risk.

Methods: Comprehensive electronic search in Pubmed, Web of Science, EBSCO, Embase, the Cochrane Library and China National Knowledge Infrastructure (CNKI) to find original articles about the association between AGT M235T polymorphism and DN risk published before 27 September 2017. Literature quality assessment was performed with the Newcastle-Ottawa Scale. Heterogeneity across studies was assessed using I^2 statistics. Random-effects model or Fixed-effects model was used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analyses to assess the influence of individual studies on the pooled estimate. Publication bias was investigated using funnel plots and Egger's regression test. Analyses were performed by using Stata 15.0.

Results: Overall, 20 eligible studies involving a total of 3822 cases and 3911 controls were included in our meta-analysis. The results showed that AGT M235T polymorphism significantly increased DN risk in recessive model (T/T versus M/T + M/M: OR = 1.35, 95%CI (1.07–1.69), I^2 = 63.8%, Z = 2.56, P = 0.010), homozygote model (T/T versus M/M: OR = 1.46, 95%CI (1.11–1.92), I^2 = 62.4%, Z = 2.69, P = 0.007) and allele model (T versus M: OR = 1.17, 95%CI (1.01–1.35), I^2 = 72.5%, Z = 2.14, P = 0.032); Subgroup analysis by ethnicity showed that AGT M235T polymorphism significantly increased DN risk in recessive model (T/T versus M/T + M/M: OR = 1.39, 95%CI (1.06–1.81), I^2 = 66.6%, Z = 2.42, P = 0.016), homozygote model (T/T versus M/M: OR = 1.47, 95%CI (1.08–2.01), I^2 = 67.7%, Z = 2.47, P = 0.013) and allele model (T versus M: OR = 1.18, 95%CI (1.02–1.37), I^2 = 69.4%, Z = 2.26, P = 0.024) in Caucasian DM population; Subgroup analysis by clinical subtype of DM also showed that AGT M235T polymorphism significantly increased DN risk in recessive model (T/T versus M/T + M/M: OR = 1.28, 95%CI (1.05–1.57), I^2 = 21.3%, Z = 2.40, P = 0.016), homozygote model (T/T versus M/M:

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OR = 1.41, 95%CI (1.04–1.92), I^2 = 30.2%, Z = 2.23, P = 0.026) and allele model (T versus M: OR = 1.14, 95%CI (1.03–1.28), I^2 = 35.5%, Z = 2.44, P = 0.015) in type 1 diabetes patients.
Conclusion: Our study showed that AGT M235T homozygous mutation significantly increase DN risk in Caucasian DM population and type 1 diabetes patients.

1. Introduction

Diabetic nephropathy (DN) is a chronic, progressive microvascular complication of diabetes mellitus (DM). It is associated with high cardiovascular morbidity and mortality and is still the most common cause of end-stage renal disease (ESRD) in developed countries [1]. Over a lifetime, DN occurs in approximately half of all patients with type 2 diabetes and one-third with type 1 diabetes [2]. In China about 30–40% of diabetes patients will develop DN [3]. DN has become a major scientific and social concern in worldwide. In spite of the main risk factors for the development of DN as hypertension and poor glycemic control, genetic susceptibility in both type 1 and type 2 DM is also of the great importance.

The renin-angiotensin-aldosterone system (RAAS), which plays an important role in regulating blood pressure, sodium and water balance, and renal homeostasis, is involved in the pathophysiology of DN [4,5]. Dysregulation of the RAAS has a critical role in the pathogenesis of DN. Excessive RAAS activation constricts renal arterioles leading to increased peripheral and renal resistance, increases glomerular capillary pressure leading to proteinuria, augments oxidative stress leading to endothelial dysfunction and so on [6,7]. These effects result in progressive renal damage and eventually lead to DN. Targeted inhibition the activation of RAAS with angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin-II-receptor blockers (ARBs), is the most common clinical strategy for slowing the disease progression [8–11]. Thus, genetic polymorphisms of these key components of RAAS provide a basis for studying the relationship between genetic variants and the development of DN [12–14].

Angiotensinogen (AGT), a rate-limiting enzyme of the RAAS, is the only known substrate for renin and is the source of all angiotensin peptides. Because the level of AGT is close to the Michaelis-Menten constant for renin, both renin and AGT levels can control the activity of the RAAS [15,16]. Recent experimental studies also have documented AGT involvement in the activation of the RAAS [17]. Genetic polymorphisms of AGT may affect the RAAS activity, which in turn affects the occurrence and development of DN. Numerous studies on the relationship between the AGT polymorphism and DN susceptibility had been conducted but the results were inconsistent. Some studies revealed a clear trend of AGT polymorphism with increased risk of DN [12,18–29], and the others suggested no association between this polymorphism and DN [30–39]. To evaluate more precisely the potential relationship between AGT polymorphism and the risk of DN, we hereby report on a meta-analysis using all available published data.

2. Materials and Methods

2.1. Search strategies

A computerized search of Pubmed, Web of Science, EBSCO, Embase, the Cochrane Library and China National Knowledge Infrastructure (CNKI) database up to 27 September 2017 was conducted using the following search strategy: ("AGT" or "angiotensinogen"), and ("polymorphism" or "variant" or "mutation"), and ("diabetic nephropathy" or "DN"). The language was restricted to English and Chinese. A manual search of references of the retrieved articles and relevant reviews was also conducted. A flowchart of information pertaining to identification, screening, eligibility, and final datasets selected was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [40].

2.2. Inclusion and exclusion criteria

In this report, the studies that investigate the association between AGT M235T polymorphism and the risk of DN were included. The inclusion criteria were (1) case-control study design, the controls were diabetes individuals without DN; (2) available genotype information of the AGT M235T polymorphism; (3) evaluated the AGT gene M235T polymorphism and the risk of DN (4) DN was defined by urinary albumin excretion >30 mg/24 h and (5) available the duration time of DM. The major criteria for exclusion of studies were: (1) not related to DN, (2) not case-control studies, (3) no useful genotype frequency data, (4) duration of diabetes was less than 5 years, (5) duration of diabetes was not match in control and case when the time less than 15 years and more than 5 years (6) duplicate of earlier publications (For studies using the same sample in different publications, only the most complete information was included following careful examination), (7) unpublished papers, dissertations, conference articles and reviews, (8) family-based studies, (9) in vitro and animal model and (10) the number of case or control was less than 10.

2.3. Data extraction

Data from each eligible studies were extracted, including author, year of publication, country of origin, ethnicity of each study population, duration of DM, classification of DM, numbers of cases and controls and numbers of cases and controls in the AGT genotypes.