Apo E Gene Polymorphism Affects Development of Type 2 Diabetic Nephropathy in Asian Populations, Especially in East Asians: An Updated Meta-Analysis

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Background: Many studies have determined the correlation between the Apolipoprotein E (APO E) gene polymorphisms and diabetic nephropathy, but their results are inconclusive.

Material/Methods: With the aim to confirm this correlation, we performed a meta-analysis of 16 studies. The dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI).

Results: The results of our study indicate that APO e2 allele among the pooled Asian populations were more likely to show high risk of DN development (e2 allele vs. e3 allele: pooled OR=1.629, 95% CI=1.010–2.628, P=0.045). For further analysis, the APO e2 allele was associated with progress of DN in the group with duration >10 years, but not in the group with duration <10 years (e2 allele vs. e3 allele: pooled OR=1.920, 95% CI=1.338–2.754, P<0.001). The APO e2 polymorphism increased the susceptibility to DN in Asian population compared with healthy people (e2 allele vs. e3 allele: pooled OR=1.629, 95% CI=1.010–2.628, P=0.045).

Conclusions: Development of DN is associated with APO E polymorphisms in Asian populations, especially in East Asians.

MeSH Keywords: Diabetic Nephropathies • Disease Susceptibility • Meta-Analysis

Abbreviations: APO E – Apolipoprotein E • DN – Diabetic nephropathy • T2D – Type 2 diabetes • SNPs – single-nucleotide polymorphisms

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Diabetic nephropathy (DN) is the leading cause of chronic renal disease and a major cause of cardiovascular mortality. Diabetic nephropathy is associated with cardiovascular disease and increases mortality of diabetic patients [1]. Diabetic nephropathy has been categorized into 2 stages: microalbuminuria and macroalbuminuria. Several factors are involved in the pathophysiology of DN, including metabolic and hemodynamic alterations, oxidative stress, activation of the renin-angiotensin system, immunoregulatory cytokines [2,3] and genetic factors. The 2 main risk factors for diabetic nephropathy are hyperglycemia and arterial hypertension, but the genetic susceptibility in type 1 and type 2 diabetes is of great importance [4]. Previous studies have shown that type 2 diabetes (T2D) is a metabolic disorder characterized by hyperglycemia, developing insulin resistance, β-cell dysfunction, and impaired insulin secretion. As the incidence of type 2 diabetes continues to rise world-wide, the personal and social burdens associated with this complication are becoming increasingly serious. A familial study has provided compelling evidence that genetic factors contribute to DN susceptibility in T2D [5] as have studies aimed at identifying the causal genes responsible for its development.

The Apolipoprotein E (APO E) gene, located on chromosome 19q13.2, has 3 common alleles – 2, 3, and 4 – coding for the 3 main isoforms of the Apo E protein: ε2 (Arg→Cys), ε3 (parent isoform), and ε4 (Arg→Cys). There are 6 common Apo E polymorphisms: Apo ε3/3, Apo ε4/4, Apo ε2/2, Apo ε3/2, Apo ε4/2, and Apo ε4/3 [6].

Many studies have investigated gene APO E polymorphism effects on susceptibility to type 2 diabetic nephropathy, and we have summarized the findings of those individual studies in the Appendix 1. Meta-analysis is a powerful method for quantitatively summarizing results from different studies. One of its advantages is to increase the sample size, which may reduce the probability that random error will result in a false-positive or false-negative association. Therefore, we performed a meta-analysis to quantitative assess the association of APO E gene polymorphisms with DN.

### Material and Methods

#### Literature search strategy

The Medline, PubMed, Embase, and Web of Science were searched (the last search was updated on June, 10, 2014 using the search terms: “Diabetic Nephropathy” or “DN”, “polymorphism”, “APO E” or “Apolipoprotein E”. All searched studies were retrieved and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant identified studies were hand-searched in addition to eligible studies. Only published studies with full-text articles were included. When more than one of the same patient populations was included in several publications, only the one with the sample size largest or the most complete study was used in this meta-analysis. A flow diagram of the study selection process is shown in Figure 1.

#### Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined by discussion. The inclusion criteria were: (1) the study aimed to examine the association between APO E polymorphisms and susceptibility to DN; (2) the design type of the study was a case-control study; (3) the study used diabetic patients without nephropathy or healthy subjects as controls; (4) the study provided the number of DN cases or controls and the frequency of APO E genotypes.

The exclusion criteria were: (1) the study did not fit the diagnosis criteria; (2) the study was conducted on animals; (3) the study was not a case-control study; (4) the study reported useless data; (5) the study focused on type 1 diabetic subjects.

#### Data extraction

All of the data were extracted independently by 2 reviewers (Yijin Lin and Jinlin Pan) according to the pre-specified selection criteria. Disagreement was resolved by discussion. The following data were extracted: control type, diabetic duration, study design, first author’s name, publication year, and number of cases with normoalbuminuria, microalbuminuria, and macroalbuminuria, and number of healthy controls.

#### Statistical analysis

Allele frequencies at the APO E single-nucleotide polymorphisms (SNPs) from the studies were determined by the allele counting
method. Statistical analysis was conducted using Stata 11.0 (StataCorp, College Station, TX) and a P-value ≤0.05 was considered to be statistically significant. Dichotomous data are presented as the odds ratio (OR) with a 95% confidence interval (CI). Statistical heterogeneity was measured using the Q-statistic (P≤0.10 was considered to be representative of statistically significant heterogeneity). We also quantified the effect of heterogeneity using the I² statistic, which measures the degree of inconsistency in the studies by calculating what percentage of the total variation across studies is due to heterogeneity rather than by chance. A fixed-effects model was used when there was no heterogeneity of the results of the trials; otherwise, the random effects model was used. For dichotomous outcomes, patients with incomplete or missing data and small-sample studies were included in the sensitivity analyses by counting them as treatment failures. To establish the effect of clinical heterogeneity between studies on the conclusions of meta-analyses, subgroup analysis was conducted on the basis of race. Several methods were used to assess the potential for publication bias. Visual inspection of asymmetry in funnel plots was conducted. Begg's rank correlation method and Egger's weighted regression method were also used to statistically assess the publication bias (P≤0.05 was considered to be representative of statistically significant publication bias).

**Results**

**Characteristics of studies**

This meta-analysis included 16 relevant studies of APO E SNPs, with 1754 cases and 3912 controls. The characteristics of each study are presented in the Appendix 1.

**Quantitative data synthesis**

The aim of this study was to use the meta-analysis method to quantitatively summarize the results from the selected individual studies. In comparing DN cases versus diabetic patients without nephropathy, our aim was to evaluate the relationship between APO E polymorphisms on the progress of diabetic patients. The carriers of the APO e2 allele were more likely to have DN than the over-all group, the East Asia group, and the Japan group, but not in the 3 other subgroups (e2 allele vs. e3 allele: over-all: pooled OR=1.669, 95% CI=1.194–2.332, P=0.003; East Asia group: pooled OR=1.667, 95% CI=1.150–2.417, P=0.007; Japan group: pooled OR=2.352, 95% CI=1.228–4.502, P=0.010. e2 group vs. e3 group: East Asia group: pooled OR=1.829, 95% CI=1.235–2.711, P=0.003; Japan group: pooled OR=3.085, 95% CI=1.852–5.140, P<0.001) (Table 1 and Figure 2)

To understand the influence of diabetes duration on the development of diabetes, we divided the included studies into 2 parts by duration of diabetes, comparing the group with >10 years duration versus the group with duration <10 years. As Table 1 and Figure 3 show, the carriers of the APO e2 allele were associated with progression of DN in the duration > 10 years group, but not in the duration <10 years group (e2 allele vs. e3 allele: pooled OR=1.920, 95% CI=1.338–2.754, P<0.001; e2 group vs. e3 group: pooled OR=1.667, 95% CI=0.946–2.936, P=0.077).

The aim of comparing DN cases and healthy people was to estimate the association of the APO E polymorphisms and susceptibility to DN. The APO e2 polymorphism increased the susceptibility to DN in the Asian population (e2 allele vs. e3 allele: pooled OR=1.629, 95% CI=1.010–2.628, P=0.045; e2 group vs. e3 group: pooled OR=1.531, 95% CI=0.964–2.432, P=0.071) (Figure 4).

To further verify the association of development of DN and APO E polymorphisms, we quantitatively summarized the results of microalbuminuria versus normoalbuminuria and macroalbuminuria versus normoalbuminuria. The meta-analysis results of these 2 comparisons supported the results above – APO e2 allele polymorphism was associated with the progression of DN (Table 2).

There were 3 prospective studies among the papers included in this meta-analysis, and the pooled results verified the conclusion of the case-control studies – the APO e2 allele polymorphism was a risk factor in the development of DN (Progression vs. Non-progression: e2 allele vs. e3 allele: pooled RR=1.636, 95% CI=1.093–2.449, P=0.017; e2 group vs. e3 group pooled RR=1.711, 95% CI=1.124–2.606, P=0.012). We found a significant difference in comparison of ‘e2 allele vs. e3 allele’ group among ‘Progression vs. Non-progression’, but there were no other result supporting this conclusion (Table 2).

**Heterogeneity**

The heterogeneity was calculated among all studies using the Q-statistic (Q>0.05) and the I² statistic (I²=0.0%). Heterogeneity was found in some groups, and the random-effects model was used.

**Sensitivity analysis**

A single study was deleted each time to investigate the influence of the individual dataset on the pooled ORs. The corresponding pooled ORs were not materially altered (data not shown), indicating that our results are statistically robust.

**Publication bias**

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature. We found no asymmetry of the funnel plot, suggesting that there was no publication bias in our meta-analysis.
### Table 1. Summary about meta-analysis on APO E polymorphisms in Asian type 2 diabetes patients (with nephropathy vs. without nephropathy).

| Comparisons          | Stratification | Subgroups | n  | OR (95% CI) | P value | Homogeneity | Publication Bias |
|----------------------|----------------|-----------|----|-------------|---------|-------------|-----------------|
|                      |                |           |    | OR           | Cl      |             |                 |
|                      |                | All       | 15 | 1.669       | 1.194–2.332 | 0.003 | 36.41       | 0.001 | 65.1 | 0.363  | 0.468  |
| e2 allele vs. e3 allele | Region       | All       | 11 | 1.667       | 1.150–2.417 | 0.007 | 28.64       | 0.001 | 65.1 | 0.350  | 0.330  |
|                      |              | East Asia | 5  | 1.248       | 0.790–1.971 | 0.343 | 11.03       | 0.026 | 63.7 | 0.462  | 0.839  |
|                      |              | Japan     | 4  | 2.352       | 1.228–4.502 | 0.010 | 6.97        | 0.073 | 56.9 | 0.089  | 0.133  |
|                      |              | Korea     | 3  | 1.988       | 0.774–5.104 | 0.153 | 1.96        | 0.161 | 49.0 | 1.000  |       |
|                      |              | Turkey    | 4  | 1.632       | 0.650–4.094 | 0.297 | 7.44        | 0.059 | 59.7 | 1.000  | 0.603  |
| Diabetes duration    | >10 years    | All       | 9  | 1.920       | 1.338–2.754 | <0.001 | 14.73       | 0.251 | 26.8 | 0.348  | 0.199  |
|                      |              | Japan     | 4  | 0.793       | 0.480–1.310 | 0.366 | 4.10        | 0.065 | 45.7 | 0.734  | 0.982  |
|                      |              | Korea     | 2  | 0.698       | 0.289–1.683 | 0.423 | 1.63        | 0.201 | 0.201 | 1.000  |       |
|                      |              | Turkey    | 4  | 1.114       | 0.696–1.783 | 0.652 | 2.02        | 0.568 | 0.568 | 0.734  | 0.350  |
|                      | <10 years    | All       | 4  | 0.793       | 0.480–1.310 | 0.366 | 4.10        | 0.065 | 45.7 | 0.734  | 0.982  |
|                      |              | Japan     | 2  | 0.698       | 0.289–1.683 | 0.423 | 1.63        | 0.201 | 0.201 | 1.000  |       |
|                      |              | Korea     | 2  | 0.698       | 0.289–1.683 | 0.423 | 1.63        | 0.201 | 0.201 | 1.000  |       |
|                      |              | Turkey    | 4  | 1.114       | 0.696–1.783 | 0.652 | 2.02        | 0.568 | 0.568 | 0.734  | 0.350  |
| Diabetes duration    | >10 years    | All       | 10 | 1.667       | 0.946–2.936 | 0.077 | 31.59       | 0.000 | 71.5 | 0.371  | 0.608  |
|                      |              | Japan     | 5  | 1.085       | 0.852–1.340 | 0.737 | 2.33        | 0.074 | 0.074 | 0.000  |       |
|                      |              | Korea     | 5  | 1.085       | 0.852–1.340 | 0.737 | 2.33        | 0.074 | 0.074 | 0.000  |       |
|                      |              | Turkey    | 5  | 1.085       | 0.852–1.340 | 0.737 | 2.33        | 0.074 | 0.074 | 0.000  |       |
|                      | <10 years    | All       | 4  | 0.756       | 0.475–1.201 | 0.236 | 3.84        | 0.005 | 59.1 | 0.451  | 0.277  |
|                      |              | Japan     | 3  | 0.756       | 0.475–1.201 | 0.236 | 3.84        | 0.005 | 59.1 | 0.451  | 0.277  |
|                      |              | Korea     | 3  | 0.756       | 0.475–1.201 | 0.236 | 3.84        | 0.005 | 59.1 | 0.451  | 0.277  |
|                      |              | Turkey    | 3  | 0.756       | 0.475–1.201 | 0.236 | 3.84        | 0.005 | 59.1 | 0.451  | 0.277  |

| e2 carrier (e2/2, e2/3 genotypes), e3 group (e3/3 genotype) and e4 group (e3/4, e4/4 genotype). |
Discussion

Diabetic nephropathy (DN) is a major contributor to the high mortality of patients with DM [23]. Several acquired risk factors, such as abnormal lipoprotein metabolism, hypertension, and hyperglycemia, have been identified for the development of DN [24]. Genetic susceptibility is thought to contribute to the pathogenesis of this complication. Studies of patients with type 2 DM have shown either that the $e2$ allele is a risk factor for DN or no association between Apo E polymorphism and DN.
Table 2. Summary about meta-analysis on APOE polymorphisms in Asian type 2 diabetes patients with nephropathy (DN vs. with nephropathy; microalbuminuria vs. normoalbuminuria; macroalbuminuria vs. normoalbuminuria; progress vs. non-progress).

| Comparisons          | Stratification | OR/RR(95% CI) | Homogeneity | Publication Bias |
|----------------------|----------------|---------------|-------------|-----------------|
|                      |                | n             | OR/RR       | P value | Q | Ph | I² (%) | P E | P F |
| ε2 allele vs. ε3 allele | DN vs. healthy | 7             | 1.629       | 1.010–2.628 | 0.045 | 12.88 | 0.045 | 53.4 | 0.230 | 0.255 |
|                      | Microalbuminuria vs. normoalbuminuria | 4 | 1.619 | 1.087–2.414 | 0.018 | 1.13 | 0.770 | 0.0 | 1.000 | 0.870 |
|                      | Macroalbuminuria vs. normoalbuminuria | 3 | 1.808 | 0.980–3.337 | 0.058 | 4.42 | 0.110 | 54.7 | 1.000 | 0.469 |
|                      | Progress vs. non-progress | 3 | RR=1.636 | 1.093–2.449 | 0.017 | 4.18 | 0.124 | 52.2 | 0.602 | 0.527 |
| ε4 allele vs. ε3 allele | DN vs. healthy | 7 | 0.929 | 0.566–1.522 | 0.079 | 20.38 | 0.002 | 70.6 | 1.000 | 0.658 |
|                      | Microalbuminuria vs. normoalbuminuria | 4 | 0.792 | 0.541–1.160 | 0.231 | 2.75 | 0.431 | 0.0 | 0.308 | 0.553 |
|                      | Macroalbuminuria vs. normoalbuminuria | 3 | 0.992 | 0.601–1.639 | 0.976 | 1.01 | 0.605 | 0.0 | 1.000 | 0.208 |
|                      | Progress vs. non-progress | 3 | RR=1.597 | 1.025–2.486 | 0.038 | 2.21 | 0.331 | 9.5 | 1.000 | 0.132 |
| ε2 group vs. ε3 group | DN vs. healthy | 7 | 1.531 | 0.964–2.432 | 0.071 | 9.76 | 0.135 | 38.6 | 0.548 | 0.352 |
|                      | Microalbuminuria vs. normoalbuminuria | 4 | 1.382 | 0.874–2.187 | 0.167 | 1.13 | 0.771 | 0.0 | 0.806 | 0.291 |
|                      | Macroalbuminuria vs. normoalbuminuria | 3 | 2.081 | 1.080–4.010 | 0.028 | 2.81 | 0.245 | 28.8 | 0.734 | 0.649 |
|                      | Progress vs. non-progress | 3 | RR=1.711 | 1.124–2.606 | 0.012 | 3.08 | 0.215 | 35.0 | 1.000 | 0.786 |
| ε4 group vs. ε3 group | DN vs. healthy | 7 | 0.927 | 0.486–1.769 | 0.819 | 26.81 | <0.01 | 77.6 | 1.000 | 0.831 |
|                      | Microalbuminuria vs. normoalbuminuria | 4 | 0.687 | 0.443–1.065 | 0.093 | 3.96 | 0.266 | 24.3 | 0.806 | 0.436 |
|                      | Macroalbuminuria vs. normoalbuminuria | 3 | 1.153 | 0.663–2.003 | 0.614 | 0.62 | 0.734 | 0.0 | 0.308 | 0.278 |
|                      | Progress vs. non-progress | 3 | RR=1.533 | 0.952–2.468 | 0.087 | 2.15 | 0.342 | 6.8 | 0.296 | 0.127 |

ε2 carrier (ε2/2, ε2/3 genotypes), ε3 group (ε3/3 genotype) and ε4 group (ε3/4, ε4/4 genotype). The progressors on DN were defined as the subjects who shifted to a higher stage of DN from that at the baseline.

Figure 4. Forest plot of the APOE polymorphism and DN (DN vs. Healthy controls; ε2 allele vs. ε3 allele).

exists in Asian populations. A study conducted in Korean patients with type 2 DM found that the Apo ε2 allele was significantly more frequent in the macroalbuminuria group compared with the normoalbuminuria group [13]. A Japanese study involving 158 patients with long-term type 2 DM obtained similar results, showing that the ε2 allele could increase the risk...
## Appendix 1. Findings of the studies included in this meta-analysis.

| Studies                  | Year | Country | Number | Conclusion |
|--------------------------|------|---------|--------|------------|
| Necip I’lhan [7]         | 2007 | Turkey  | 37     | In conclusion, the present prospective study indicates that the e4 allele of the Apo E polymorphism is one of the prognostic risk factors involved in the development of DN with type 2 diabetes mellitus |
| Shin-ichi Araki [8]      | 2003 | Japan   | 31     | Our follow-up study indicates that the e2 allele of the Apo E polymorphism is a prognostic risk factor for both the onset and the progression of diabetic nephropathy in Japanese type 2 diabetes |
| Masaaki Eto [9]         | 2001 | Japan   | 99     | Apo E2 is a positive factor and apo E4 is a negative factor for diabetic nephropathy. Apo E2 TG-rich lipoproteins, including remnant lipoproteins, affected HMCs. Remnant lipoproteins may have an important role in the progression of diabetic nephropathy |
| Kai-Jen Tien [10]       | 2011 | China   | 136    | Our study suggests the apo E4 carrier might serve as a predictor of DN progression in Taiwan |
| Kazutoshi Horita [11]   | 1994 | Japan   | 57     | It is concluded that apo E2 is associated with renal insufficiency in NIDDM and that apo E2 may be a factor that aggravates lipid abnormalities in NIDDM with renal failure |
| Mi-Kwang Kwon [12]      | 2007 | Korea   | 36     | The carrier might be E4 and carry with the protection for the development of diabetic nephropathy in type 2 diabetic patients without respect to dyslipidemia |
| Sung kyu Ha [13]        | 1999 | Korea   | 74     | Apo E2 allele and E2 carrier frequencies were significantly higher in macroalbuminuria group. These results suggest that E2 allele may be associated with the development of clinical albuminuria in Korean patients with NIDDM |
| Ng MCY [14]             | 2006 | China   | 366    | Our findings suggest the importance of interactions among lipid genes in modulating the risk of DN |
| Kadiye Altok Reis [15]  | 2010 | Turkey  | 106    | Our study has shown that AGT M235T TT genotype and APOE e2/e3 genotype may be linked to a risk for DN among Turkish population |
| Limei Liu [16]          | 2003 | China   | 218    | These results suggest that the HSPG T allele is a risk factor for the development of severe diabetic nephropathy in type 2 diabetic patients, and that the Apo E2 allele is a risk factor for the occurrence of type 2 diabetes mellitus in Chinese general population. In addition, we find that co-inheritance of T/E2 confers a higher risk of type 2 diabetes mellitus progression to diabetic nephropathy in Chinese |
| Ming-chia Hsieh [17]    | 2002 | China   | 215    | These findings imply that apo E polymorphism is apparently related to the development of DN in type 2 diabetes in Taiwan |
| Eto M. [18]             | 1995 | Japan   | 146    | It is concluded that is a possibility that the e2 allele is associated with nephropathy in NINNM |
| Hideki Kimura [19]      | 1997 | Japan   | 81     | Results indicate that apolipoprotein E polymorphism is associated with the progression of diabetic nephropathy. Presence of the apolipoprotein E4 allele is a protective factor, and other alleles are risk factors |
| M. Erdogan [20]         | 2009 | Turkey  | 46     | We conclude that the Apo E gene polymorphism is not associated with the development of diabetic nephropathy in Turkish Type 2 diabetic patients. Lack of association between Apo E gene polymorphism and Type 2 diabetic nephropathy might be due to ethnic differences |
| Shuk-Woon Ma [21]       | 2008 | China   | 112    | The APOE e2 allele does not seem to be associated with increased risk of renal impairment in Chinese type 2 diabetic patients. Plasma lipid-standardized α-tocopherol may play a role in determining risk of renal dysfunction in type 2 diabetes |
| Akarsu E. [22]          | 2001 | Turkey  | 24     | As a result, we concluded that the e2 allele of apo E may play a role in the mechanism of nephropathy in type 2 diabetes mellitus |
of DN, and ε4 was a protective factor [9]. Conversely, there are conflicting results regarding the impact of allele ε2 and ε4 on the development of DN. The APO ε2 allele did not appear to be associated with increased risk of renal impairment in Chinese type 2 diabetic patients [21] and a study indicated that the ε4 allele of the Apo E polymorphism is one of the prognostic risk factors involved in the development of DN with type 2 diabetes mellitus [7].

The results of this study suggest that APO ε2 allele is more likely to increase the risk of DN, while APO ε4 allele is not associated with the DN development and susceptibility in an East Asia population. Specifically, the OR value of most included studies (3/15) were larger than 1 when the ε2 allele and APO ε3 was compared (Figure 2). This finding indicates that the negative results of those studies might be due to inadequate sample size. In addition to the sample size, another reason for this inconsistency is the duration of diabetes in the DN and non-DN groups. This meta-analysis shows that, in most individual studies in patients with diabetes duration >10 years group, there is a significant correlation between DN and APO ε2, but none of the studies had positive results in subgroups of patients with diabetes duration <10 years (Figure 3). The defective ability of the APO ε2 isofrom to bind to Apo E receptors may increase the risk of DN.

There are some limitations to this study. Firstly, because only published studies were included in the meta-analysis, publication bias may have occurred, even though it was not found by statistical tests. Secondly, a meta-analysis essentially retains the methodological deficiencies of the included studies. Finally, this meta-analysis is based on unadjusted estimates, while a more precise analysis could be performed if individual data were available.

**Conclusions**

In conclusion, in spite of several limitations mentioned above, this meta-analysis suggests that APO ε2 mutation increased the development of DN, especially in East Asian populations.

**Conflicts of interest**

None.

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