Family history and renin-angiotensin system gene polymorphisms in Chinese patients with type 2 diabetes mellitus

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Abstract
A positive family history is recognized as an important risk factor for type 2 diabetes mellitus (T2DM), but the association of family history with rennin-angiotensin system (RAS) gene polymorphisms has not been reported yet, thus we aim to investigate it.

Family history records, clinical and biochemical data were obtained from 1239 T2DM patients. Polymerase chain reaction (PCR) was performed for angiotensin-converting enzyme (ACE) genotyping and PCR-restricted fragment length polymorphism was used for angiotensinogen (AGT) genotyping.

Patients with a negative family history had higher level of triglyceride and blood pressure, whereas those with a positive family history showed younger onset age and lower body mass index value (All $P<.05$), these findings were age-dependent. The percentage of hypertension was lower with a higher percentage of overweight among the patients with a positive family history (All $P<.05$). Patients with a positive family history and those with a negative family history had comparable genotype and allele distribution of ACE gene insertion/deletion polymorphisms and AGT gene M/T polymorphisms.

A positive family history of diabetes was not associated with the RAS gene polymorphisms.

Abbreviations: ACE = angiotensin-converting enzyme, AGT = angiotensinogen, BMI = body mass index, BP = blood pressure, DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA1c = glycated hemoglobin, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, MAP = mean arterial pressure, PCR = polymerase chain reaction, RAS = rennin-angiotensin system, RFLP = restricted fragment length polymorphism, SBP = systolic blood pressure, T2DM = type 2 diabetes mellitus, TC = total cholesterol, TG = triglycerides, WC = waist circumference, WHR = waist-to-hip ratio.

Keywords: angiotensin converting enzyme, angiotensinogen, family history, gene polymorphism, hypertension, obesity, type 2 diabetes mellitus

1. Introduction
Precise mechanism for diabetes is still ambiguous though the pathological and etiological factors have been extensively investigated. Interactions of genetic and environment factors, as one of the inference, arose researchers’ attention.\textsuperscript{[1]} Gene inheritance from parents is considered as a significant risk factor for diabetes, but which is the major predominant side is still unclear (maternal, paternal, or both of them?). Reports including excess of maternal transmission and absence of excess of maternal transmission are reported in Asians, South Americans, and Europeans.\textsuperscript{[2–5]} The contradictory conclusions may associate with genetic components directly or indirectly.

Recently, genetic variants in rennin-angiotensin system (RAS) have been studied extensively and controversial findings existed in several studies.\textsuperscript{[6–7]} Subsequently, an increased activity of RAS has been noticed in the development of insulin resistance and type 2 diabetes mellitus (T2DM). However, the distribution analysis of angiotensin-converting enzyme (ACE) and angiotensinogen (AGT) gene polymorphisms in patients with T2DM according to family history is rare to see, thus we aim to investigate it.

2. Subjects and methods
2.1. Study design and subjects
A cross-sectional association study was designed and participants were newly diagnosed T2DM patients between January 2012 and September 2016 from the affiliated hospitals. The Institutional Review Board of the Guilin Medical University Affiliated Hospital approved this study (GLMC191211HL), and each patient gave written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki. Diagnosis of T2DM was based upon the American Diabetes
Association (ADA) criteria.\[8\] We performed a study’s power calculation and found that a sample size of 513 subjects was sufficient for a proper evaluation of the validity of the findings. Here we included data from 1239 patients to validate our hypothesis. All the patients were newly diagnosed and naive to any antidiabetic or antihypertensive medications.

2.2. Clinical data and family information collection

In this study, we excluded patients with autoimmune type 1 diabetes, diabetes undergoing surgery, in pregnancy or those with diabetic complication at the hospital administration. Family history was recorded by face-to-face interview with the help of professional nursing staff. Patients were asked whether their biological mother and/or father had (whether alive or deceased) previously been diagnosed with diabetes. Parental history of diabetes was categorized as a negative family history and a positive family history (maternal only, paternal only or both). All diabetes was categorized as a negative family history and a previously been diagnosed with diabetes. Parental history of diabetes, diabetes undergoing surgery, in pregnancy or those with diabetic complication at the hospital administration. Family history was recorded by face-to-face interview with the help of diabetic complication at the hospital administration. Family history was recorded by face-to-face interview with the help of parental history of diabetes, diabetes undergoing surgery, in pregnancy or those with diabetic complication at the hospital administration. Family history was recorded by face-to-face interview with the help of family.

2.4. Statistic analysis

All data were expressed as means ± standard deviation (SD), frequency or percent, as appropriate. Hardy-Weinberg equilibrium was calculated using the gene-counting method and difference was assessed by $\chi^2$ test. The t-test and Mann-Whitney rank sum test (MW) were adopted for comparison of 2 numerical variables when data were normally and not normally distributed, accordingly. Analysis of covariance (ANCOVA) adjusting for age was applied whenever appropriate. All data were carried out using the PASW Statistics software 18.0.0 (IBM Corp., Chicago, IL). A 2-tailed $P < .05$ was considered to be statistically significant.

3. Results

3.1. Sample characteristics

Among the 1239 patients included in this study, 27.36% (339) patients had a positive family history, 43.05% (486) men, 40.19% (498) hypertensive, and 66.34% (822) overweight defined by a BMI value more than 23.0kg/m². The frequency of the I and D alleles was 67.31% and 32.69%, respectively. Whereas those of the M and T alleles was 15.50% and 84.50%, respectively. We compared the observed genotype frequencies achieved from the data and the expected genotype frequencies obtained from the Hardy-Weinberg equilibrium via $\chi^2$. The calculated $P$ values of $\chi^2$ was $P=.540$ for ACE, and $P=.999$ for AGT, indicating a homogeneous and representative sample population. The genotype frequencies were 43.10% for ID, 45.76% for II, 11.14% for DD, 2.34% for MM, 71.35% for TT, and 26.31% for MT accordingly.

3.2. Clinical and biochemical characteristics relating to family history

Table 1 shows the baseline characteristics of patients. A total of 339 patients in this population had a positive family history. A positive family history was defined by father alone, mother alone, and both of them. Clinical data revealed that patients with a negative family history had higher TC, HDL-C, SBP, DBP, MAP, and both of them. Clinical data revealed that patients with a negative family history had higher TC, HDL-C, SBP, DBP, MAP, and both of them. Clinical data revealed that patients with a negative family history had higher TC, HDL-C, SBP, DBP, MAP, and both of them. Clinical data revealed that patients with a negative family history had higher TC, HDL-C, SBP, DBP, MAP, and both of them.

3.3. Association of the renin-angiotensin system genetic polymorphisms with family history

Tables 2 and 3 show the genotype and allele frequencies of RAS genetic polymorphisms relating to family history. No differences were significant. A positive family history had no significant impact on the genotype and allele distribution of ACE gene I/D polymorphisms and AGT gene M/T polymorphisms. The finding remained consistent when the 2 polymorphisms were combined.
### Table 1
Clinical and biochemical characteristics of the type 2 diabetes mellitus patients based on family history.

| NFH | FH | P   | P*  |
|-----|----|-----|-----|
| Patients (n) | 900 | 339 | –   | –   |
| MM | 350 | 550 | 136:203 | 1.166 |
| Age, y | 4.00(1.00–10.00) | 4.00(1.00–8.00) | <.001 |
| WHR | 0.88 ± 0.13 | 0.84 ± 0.14 | <.001 |
| DBP, mmHg | 80.48 ± 11.51 | 79.29 ± 11.11 | .035 |
| SBP, mmHg | 136.50 ± 22.38 | 125.23 ± 19.37 | .004 |
| BMI, kg/m² | 24.32 ± 3.95 | 25.30 ± 4.38 | <.001 |
| Triglycerides, mmol/L | 1.38(0.93–2.02) | 1.28(0.90–2.04) | .022 |
| HDL-C, mmol/L | 1.23(1.03–1.47) | 1.18(0.98–1.39) | .006 |

Data are shown as means ± SD, median (interquartile range).

* Derived from Mann-Whitney rank sum test.

### 3.4. Association of family history with hypertension and BMI-defined obesity

Table 4 shows the percentages of hypertension and BMI-defined obesity stratified by family history. The percentage of hypertension (46.2% vs 24.2%, P < .001) was significantly higher in patients with a negative family history. Although the patients with a positive family history demonstrated statistical significant higher percentage of BMI-defined obesity (65.0% vs 71.1%, P = .043).

### Table 2
The genotype frequencies of renin-angiotensin system gene polymorphisms according to family history.

| Genotypes and alleles | NFH | FH | Comparison | P  |
|----------------------|-----|----|------------|----|
| ACE | II | 404 (44.9) | 163 (48.1) | II vs DI+DD | .314 |
| ID | 395 (43.9) | 139 (41.0) | DI vs DD+II | .361 |
| DD | 101 (11.2) | 37 (10.9) | DD vs DI+II | .678 |
| Total | 900 (100) | 339 (100) | – | .593 |
| I | 1203 (66.8) | 465 (66.8) | D vs I | .408 |
| D | 597 (33.2) | 213 (31.4) | – | .080 |
| Total | 1800 (100) | 678 (100) | – | .080 |

Data are shown as number (percentage). P value is derived by the χ² test.

### 4. Discussion

Here we have reported none of significant effects of a positive T2DM family history on hypertension and overweight among T2DM patients. Interestingly, differential effects were noticed in hypertension and overweight based on family history, that lower percentage for hypertension and a higher percentage for overweight were noticed among the patients with a positive family history. Furthermore, we showed that the different effects resulted from a positive family history were not influenced by the ACE gene I/D polymorphisms and AGT gene T/M polymorphisms.

According to previous studies, the polymorphisms of RAS components were demonstrated to increase the risk of diabetes, obesity and hypertension among various ethnics and evidence-based medicine.[19–22] In this study, we have found that the RAS polymorphisms and a positive T2DM family history were not mutually associated.
Family trait is a common recognition for type 2 diabetes. Indeed, a positive family history of T2DM contrasts any genetic influences to exert far more impacts on individual’s development of diabetes.[21] Genetic transmission can explain in a way that patients with a positive family history were diagnosed at a younger age, indicating an early-onset age. Of interest, the levels of lipids and blood pressures in patients with a positive family history seem to be lower than the patients with a negative family history. The most likely explanation is that a family history of T2DM contrasts any genetic influences to exert far more impacts on individual’s development of diabetes.[21] Genetic transmission can explain in a way that patients with a positive family history were diagnosed at a younger age, indicating an early-onset age. Of interest, the levels of lipids and blood pressures in patients with a positive family history seem to be lower than the patients with a negative family history. The most likely explanation is that a family history reveals elements of lifestyle and thus is more powerful than genetic factors. Based on our findings, the percentage of hypertension in a negative family history was nearly two folds of that in those with a positive family history. And the odds ratio of overweight was 1.324 with marginal P value significance. Those patients with a positive T2DM family history might have better awareness of the disease and thus could see doctors for tests of diabetes and an earlier diagnosis.[24] Previously we have shown that the relationship of obesity and ACE gene I/D polymorphisms was not significant in Chinese T2DM patients.[12] And a review on the relationship of ACE gene I/D polymorphisms and hypertension including 12 positive and 14 negative studies concluded that ACE might play a secondary rather than primary role in hypertension.[23] Another study failed to present any association between the M/T polymorphisms and hypertensive phenotype.[26] Besides, parental-paternal and/or maternal-transmission of diabetes play a key role in determining of increased risk of diabetes.[27-28] In addition, previous studies from different regions of the world have shown that there is an excess maternal transmission or paternal transmission of diabetes, albeit all these studies have not explored the role of the RAS polymorphisms.[25,26] However, we did not observe a difference in the percentage of hypertension and overweight in those T2DM patients with a positive paternal or maternal history (supplement data, http://links.lww.com/MD/C29).

### Table 5

The association between family history and renin-angiotensin system gene polymorphisms based on hypertension.

|                      | Hypertensive patients with type 2 diabetes | Nonhypertensive patients with type 2 diabetes |
|----------------------|-------------------------------------------|-----------------------------------------------|
|                      | NFH | FH | P     | NFH | FH | P     |
| II                   | 195 (46.9)  | 43 (52.4)  | .357 | 209 (43.2)  | 120 (46.7)  | .360 |
| ID                   | 174 (41.8)  | 31 (37.8)  | .499 | 221 (45.7)  | 108 (42.0)  | .343 |
| DD                   | 47 (11.3)  | 8 (9.8) | .684 | 54 (11.2)  | 29 (11.3)  | .968 |
| Total                | 416 (100)  | 82 (100)  | .650 | 484 (100)  | 257 (100)  | .616 |
| I                    | 564 (67.8)  | 117 (71.3)  | .371 | 329 (34.0)  | 166 (32.3)  | .511 |
| D                    | 268 (32.2)  | 47 (28.7) | .371 | 329 (34.0)  | 166 (32.3)  | .511 |
| Total                | 832 (100)  | 164 (100)  | .968 | 102 (100)  | 514 (100)  | .616 |
| MM                   | 11 (2.6)  | 0 (0.0) | .137 | 11 (2.3)  | 7 (2.7)  | .704 |
| MT                   | 103 (24.8)  | 26 (31.7)  | .228 | 128 (26.4)  | 69 (26.8)  | .906 |
| TT                   | 302 (72.6)  | 56 (68.3)  | .428 | 345 (71.3)  | 181 (70.5)  | .059 |
| Total                | 416 (100)  | 82 (100)  | .164 | 484 (100)  | 257 (100)  | .919 |
| M                    | 125 (15.0)  | 26 (15.9) | .137 | 11 (2.3)  | 7 (2.7)  | .704 |
| T                    | 707 (85.0)  | 138 (84.1)  | .786 | 818 (84.5)  | 431 (83.9)  | .743 |
| Total                | 832 (100)  | 164 (100)  | .968 | 102 (100)  | 514 (100)  | .616 |

Data are shown as number (percentage). P value is derived by the x^2 test. The definition of hypertension is: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. DBP = diastolic blood pressure, FH = family history, NFH = no family history, SBP = systolic blood pressure.

### Table 6

The association between family history and renin-angiotensin system gene polymorphisms based on BMI defined obesity.

|                      | Patients with normal BMI | Patients with overweight |
|----------------------|--------------------------|--------------------------|
|                      | NFH | FH | P     | NFH | FH | P     |
| II                   | 137 (43.5)  | 48 (47.1)  | .529 | 267 (45.6)  | 115 (48.5)  | .453 |
| ID                   | 142 (45.1)  | 39 (38.2)  | .226 | 253 (43.2)  | 100 (42.2)  | .782 |
| DD                   | 36 (11.4)  | 15 (14.7) | .582 | 65 (11.1)  | 22 (9.3)  | .440 |
| Total                | 315 (100)  | 102 (100)  | .601 | 565 (100)  | 257 (100)  | .645 |
| I                    | 416 (66.0)  | 135 (66.2)  | .970 | 787 (67.3)  | 330 (69.6)  | .534 |
| D                    | 214 (34.0)  | 69 (33.8)  | .970 | 383 (27.7)  | 144 (30.4)  | .354 |
| Total                | 630 (100)  | 204 (100)  | 1710 | 474 (100)  | .453 |
| MM                   | 6 (2.0)  | 4 (3.9)  | .042 | 16 (2.7)  | 3 (1.3)  | .204 |
| MT                   | 83 (26.3)  | 26 (25.5)  | .042 | 148 (25.3)  | 69 (29.1)  | .260 |
| TT                   | 226 (71.7)  | 72 (70.6)  | .022 | 421 (72.5)  | 165 (69.8)  | .501 |
| Total                | 315 (100)  | 102 (100)  | .511 | 565 (100)  | 257 (100)  | .268 |
| M                    | 95 (15.1)  | 34 (16.2)  | .180 | 180 (15.6)  | 75 (15.6)  | .824 |
| T                    | 535 (84.9)  | 170 (83.3)  | .586 | 990 (84.6)  | 399 (84.2)  | .824 |
| Total                | 630 (100)  | 204 (100)  | 1170 | 474 (100)  | .453 |

Data are shown as number (percentage). P value is derived by the x^2 test. The definition of overweight is, normal: BMI < 23 kg/m², overweight: BMI ≥ 23 kg/m². BMI = body mass index, FH = family history, NFH = no family history.
As a result, diabetes is influenced dominantly by multiple genetic and environmental factors. Family history of diabetes indicates that beyond the genetic heritability, parents, and their children share common lifestyle behaviors.\(^5\,6\) Thus, we propose that, apart from taking genetic factors into consideration, everybody should develop a healthier behavior at usual, especially the T2DM patients.

The limitation of this study included the following. First, some parents showed later onset age of T2DM than their children and thus suggested publication bias. Second, we did not record about the prevalence of diabetes among patients’ grandparents and siblings, and thus our prevalence of diabetes with positive family history is lower than the overall population. Third, family history that should take both genetic factors and lifestyle into account, but we just pay attention to genetic factors here. Thus, a deep study is still needed.

In conclusion, the RAS gene polymorphisms had little impacts on hypertension and overweight in T2DM patients with a positive family history.

5. Authors’ contribution

H-LZ designed the study, revised the article and approved for the submission. Y-HP wrote the article. Y-MH and Y-CQ performed the data analyses with assistance from coauthors, WI, and L-JG did laboratory works at the Center for Diabetic Systems Medicine, Guangxi Key Laboratory of Excellence, Guilin Medical University, X-XZ and J-LX involved in recruiting volunteers at the Affiliated Hospital of Guilin Medical University. This study was supported by grants from the National Natural Science Foundation of China (81270934, 81471054) and the Innovation Project of Guangxi Graduate Education (JGY2015128).

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