Association of Pentraxin 3 Gene Polymorphisms with Susceptibility to Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a major microvascular complication of diabetes. Pentraxin 3 (PTX3) is a member of the acute-phase reactants superfamily and altered plasma levels of PTX3 are associated with DN. We performed a case-control study to analyze the relationship between single nucleotide polymorphisms (SNPs) in PTX3 and the risk for DN in patients with type 2 diabetes.

Material/Methods: The study included 135 DN patients, 155 non-diabetic nephropathy (NDN) patients, and 152 normal controls (NC) (N=442). We genotyped eight PTX3 SNPs (rs2305619, rs2120243, rs1456099, rs7634847, rs1840680, rs2316706, rs2316709, and rs7616177) using the ABI PRISM SNapshot method.

Results: The genotype frequencies of rs2305619 and rs2120243 differed significantly between the DN and the NDN groups (p=0.017 and p=0.033, respectively). Patients with the GG variant of rs2305619 showed 4.078-fold higher susceptibility to DN than those with the AA variant (OR=4.078, 95% CI=1.370–12.135, p=0.012); patients with the AA variant of rs2120243 had a lower risk of developing DN (OR=0.213, 95% CI=0.055–0.826, p=0.025). Haplotype analysis showed an association between the CAGGG haplotype in block 1 with DN (p=0.0319).

Conclusions: Our findings suggested that PTX3 polymorphisms were associated with an increased risk for DN in Chinese patients with type 2 diabetes.

MeSH Keywords: Diabetes Mellitus, Type 2 • Diabetic Nephropathies • Polymorphism, Single Nucleotide

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Background

Diabetes and diabetic nephropathy (DN), a major and specific microvascular complication of diabetes, are increasingly prevalent and have become serious health problems. DN exhibits a high incidence rate in patients with diabetes and remains the main cause of end-stage renal disease [1].

Although the mechanisms by which diabetic patients develop DN are not completely understood, hyperglycemic exposure, hypertension, and other factors such as high levels of advanced glycation end products, oxidative stress, inflammation, and protein kinase C are generally considered to be risk factors for DN. The Steno-2 study showed that strict metabolic control can effectively inhibit the progression of DN [2]. However, some individuals suffer from DN despite rigid metabolic control. The limited efficacy of current interventions, familial aggregation of DN, and clustering of DN within ethnic groups indicate that a genetic factor may contribute to susceptibility to DN [3].

Pentraxin 3 (PTX3), a form of long pentraxin, is a member of the acute-phase reactant superfamily and shares structural homology with short pentraxins, such as C-reactive protein (CRP) and serum amyloid P component [4]. PTX3 is produced by several cell types, most prominently by endothelial cells and monocytes, in response to inflammation. PTX3 is a sensitive biomarker of localized inflammatory reactions [4,5] and is associated with a variety of clinical diseases, including coronary artery disease, rheumatoid arthritis, sepsis [5], and chronic kidney diseases (CKD) [6,7]. Previous studies have suggested that DN is a low-grade chronic inflammatory disease [8,9]. Altered plasma levels of PTX3 are associated with development of DN [6,10,11]; plasma PTX3 levels are inversely associated with eGFR, but positively associated with levels of albuminuria/proteinuria in patients with DN. Hence, PTX3 may be implicated in the development of DN.

Single nucleotide polymorphisms (SNPs) in PTX3 have been found to influence circulating PTX3 levels [10,12–15] and are associated with the risk of some diseases, including primary graft dysfunction after lung transplantation [13], pulmonary tuberculosis [16], and development of hepatocellular carcinoma in patients with chronic hepatitis C (CHC) [15]. However, no data are available on the association between PTX3 polymorphisms and DN in patients with diabetes. Previous studies have shown that certain regions on chromosome 3q are associated with an increased susceptibility to DN, based on genome-wide scanning and linkage analysis [17,18]. PTX3 is located on chromosome 3 at band q25. We hypothesized that variants of PTX3 may be associated with an increased risk of developing DN. The primary goal of the present study was to assess the relationship between PTX3 variants and DN in Han Chinese patients with type 2 diabetes.

Material and Methods

Participants

A total of 442 participants were recruited from the First Affiliated Hospital of Wenzhou Medical University between December 2015 and June 2016 for this case-control study. They included 290 patients known to have type 2 diabetes for longer than five years and 152 gender-matched normal controls (NC). All participants were unrelated and of Han Chinese ethnicity. Eligible patients with type 2 diabetes were categorized into two groups: the non-diabetic nephropathy (NDN) group (n=155) and the diabetic nephropathy (DN) group (n=135). Patients with type 2 diabetes were diagnosed according to the diagnostic criteria of the American Diabetes Association (ADA) published in 2016 [19]. Albuminuria was determined according to the urine albumin-to-creatinine ratio (ACR) suggested by the ADA [19]. Estimation of the glomerular filtration rate (eGFR) was performed using the Chronic Kidney Disease Epidemiology Collaboration formula. DN was defined on the basis of persistent microalbuminuria detected during at least two examinations (ACR >30 mg/g) or overt albuminuria (ACR >300 mg/g), with or without eGFR <60 mL/min/1.73 m² and in the presence of diabetic retinopathy. Patients with another kidney diseases, inflammatory diseases, pregnancy, or congestive heart disease were excluded from the study. Patients with ACR <30 mg/g and eGFR >60 mL/min/1.73 m² were considered NDN.

All procedures were performed in accordance with the Declaration of Helsinki and informed consent was obtained from each individual. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

Genotyping

Samples of whole blood were collected from each participant. Genomic DNA was extracted using a DNA Purification Kit (TIANNamp Blood DNA Kit; Tiangen Biotech, China), according to the manufacturer’s instructions. Individual DNA samples were genotyped using the ABI PRISM SNAPSHOT method (Applied Biosystems, CA, USA). Eight SNPs (rs2305619, rs2120243, rs1456099, rs7634847, rs1840680, rs2316706, rs2316709, and rs7616177) in PTX3 were analyzed. The SNAPSHOT reactions were performed in a total reaction volume of 8 µL containing SNAPSHOT Multiplex reagent (5 µL), extended primer mix (1 µL), and templates (2 µL), which consisted of purified multiplex polymerase chain reaction (PCR) products. The extension products were purified by incubation with 1 unit of shrimp alkaline phosphatase (SAP) at 37°C for 60 minutes and a subsequent incubation at 85°C for 15 minutes for enzyme inactivation. The purified products (1 µL), GeneScan-120
Table 1. The baseline characteristics of subjects among DN, NDN and NC group.

| Parameters                  | NC (n=152) | NDN (n=155) | p<sup>a</sup> | DN (n=135) | p<sup>b</sup> | p<sup>b</sup> |
|-----------------------------|------------|-------------|--------------|------------|--------------|--------------|
| Male/Female                 | 67/85      | 81/74       | 0.152        | 68/67      | 0.286        | 0.748        |
| Age (years)                 | 59.4±11.4  | 59.6±10.5   | 0.854        | 62.5±11.17 | 0.022        | 0.027        |
| Course of diabetes (years)  | –          | 11.8±4.6    |              | 13.1±7.7   |              | 0.041        |
| HbA1C (mmol/L)              | 5.66±0.36  | 9.51±8.51   | <0.001       | 9.12±2.09  | <0.001       | 0.579        |
| Hypertension                | 66 (43.4%) | 82 (52.9%)  | 0.096        | 108 (80.0%)| <0.001       | <0.001       |
| FPG (mmol/L)                | 5.35±0.58  | 7.18±2.84   | <0.001       | 8.37±12.67 | 0.004        | 0.290        |
| TC (mmol/L)                 | 5.18±1.05  | 4.70±1.24   | <0.001       | 5.07±1.64  | 0.475        | 0.031        |
| TG (mmol/L)                 | 1.68±1.33  | 1.97±1.41   | 0.057        | 2.16±1.98  | 0.015        | 0.375        |
| HDL (mmol/L)                | 1.29±0.31  | 1.11±0.31   | <0.001       | 1.13±0.38  | <0.001       | 0.616        |
| LDL (mmol/L)                | 2.96±0.85  | 2.64±0.89   | 0.002        | 2.79±1.15  | 0.152        | 0.239        |
| eGFR (mL/min/1.73 m<sup>2</sup>) | 98.3±14.1 | 100.8±18.8 | 0.073        | 91.1±20.4  | <0.001       | 0.055        |
| LnACR (mg/g)                | –          | 1.89±0.76   | –            | 5.44±1.68  | –            | <0.001       |

NC – normal control; DN – diabetic nephropathy; NDN – non-diabetic nephropathy; HbA1c – glycosylated hemoglobin; FPG – fasting plasma glucose; TC – total cholesterol; TG – triglyceride; HDL – high-density lipoprotein; LDL – low-density lipoprotein; eGFR – estimated glomerular filtration rate; LnACR – Log<sub>10</sub> transformation of albumin-to-creatinine ratio. * Comparing the NC group with the NDN group; * Comparing the NC group with the DN group; † Comparing the DN group with the NDN group.

Results

Baseline characteristics

The baseline characteristics of the study participants in the DN, NDN, and NC groups are shown in Table 1. The groups showed no significant differences in gender ratio (p>0.05). Patients in the DN group were older than those in the NDN and NC groups (p<0.05). The proportion of patients with hypertension was significantly higher in the DN group than in the NDN and NC groups (p<0.01). Compared with the NDN group, patients in the DN group had a longer duration of diabetes (p=0.041). The levels of fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) in patients with diabetes were significantly higher than those of patients in the NC group (all p<0.01). eGFR was lower in the DN group than in the NC group (p<0.01).

Associations between PTX3 SNPs and DN in patients with T2DM

As shown in Table 2, the genotype frequencies of rs2305619 differed significantly between the DN and the NDN groups (p<0.05), and the allele frequencies of rs2305619 differed significantly between the DN and the NDN groups (p<0.05). Patients with the GG variant showed 4.078-fold higher susceptibility to DN than those with the AA variant (OR=4.078, 95% CI=1.370–12.135, p=0.012, Table 3). The genotype frequencies
Table 2. The distributions of genotype and allele of PTX3 SNPs in patients with diabetic nephropathy (DN group), non-diabetic nephropathy (NDN group) and normal controls (NC group) (n/%).

| Genotypes/Allele | NC (n=152) | NDN (n=155) | P* | DN (n=135) | P* | P* |
|------------------|------------|-------------|----|------------|----|----|
| rs2305619        |            |             |    |            |    |    |
| GG               | 62 (40.8%) | 52 (33.5%)  | 0.339 | 55 (40.7%) | 0.008 | 0.017 |
| GA               | 69 (45.4%) | 83 (53.5%)  | 75 (55.6%) |
| AA               | 21 (13.8%) | 20 (13.4%)  | 5 (3.7%) |
| G                | 193 (63.5%) | 187 (60.3%) | 0.420 | 185 (68.5%) | 0.204 | 0.040 |
| rs2120243        |            |             |    |            |    |    |
| A                | 111 (36.5%) | 123 (39.7%) | 85 (31.5%) |
| CC               | 68 (44.7%) | 55 (35.5%)  | 0.200 | 61 (45.2%) | 0.038 | 0.033 |
| CA               | 70 (46.1%) | 87 (56.1%)  | 71 (52.6%) |
| AA               | 14 (9.2%)  | 13 (8.4%)   | 3 (2.2%) |
| C                | 206 (66.8%) | 198 (63.9%) | 0.309 | 193 (71.5%) | 0.345 | 0.051 |
| rs1456099        |            |             |    |            |    |    |
| T                | 112 (36.1%) | 112 (36.1%) | 77 (28.5) |
| TT               | 40 (26.3%) | 48 (31.0%)  | 0.493 | 35 (25.9%) | 0.907 | 0.605 |
| TA               | 73 (48%)   | 75 (48.4%)  | 68 (50.4%) |
| AA               | 39 (25.7%) | 32 (20.6%)  | 32 (23.7%) |
| T                | 153 (50.3%) | 171 (55.2%) | 0.230 | 138 (51.1%) | 0.852 | 0.329 |
| rs7634847        |            |             |    |            |    |    |
| A                | 151 (49.7%) | 139 (44.8%) | 132 (48.9%) |
| GG               | 94 (61.8%) | 94 (60.6%)  | 0.952 | 89 (65.9%) | 0.534 | 0.370 |
| GA               | 53 (34.9%) | 55 (35.5%)  | 44 (32.6%) |
| AA               | 5 (3.3%)   | 6 (3.9%)    | 2 (1.5%) |
| G                | 241 (79.3%) | 243 (78.4%) | 0.787 | 222 (82.2%) | 0.372 | 0.248 |
| rs1840680        |            |             |    |            |    |    |
| A                | 63 (20.7%) | 67 (21.6%)  | 48 (17.8%) |
| GG               | 67 (44.1%) | 54 (34.8%)  | 0.189 | 59 (43.7%) | 0.134 | 0.123 |
| GA               | 66 (43.4%) | 83 (53.5%)  | 68 (50.4%) |
| AA               | 19 (12.5%) | 18 (11.6%)  | 8 (5.9%) |
| G                | 200 (65.8%) | 191 (61.6%) | 0.282 | 186 (68.9%) | 0.430 | 0.067 |
| rs2316706        |            |             |    |            |    |    |
| A                | 104 (34.2%) | 119 (38.4%) | 84 (31.1%) |
| GG               | 70 (46.1%) | 58 (37.4%)  | 0.260 | 60 (44.4%) | 0.112 | 0.136 |
| GT               | 63 (41.4%) | 78 (50.3%)  | 67 (49.6%) |
| TT               | 19 (12.5%) | 19 (12.3%)  | 8 (9.3%) |
| G                | 203 (66.8%) | 194 (62.6%) | 0.277 | 187 (69.3%) | 0.525 | 0.091 |
| rs2316709        |            |             |    |            |    |    |
| T                | 101 (33.2%) | 116 (37.4%) | 83 (30.7%) |
| AA               | 65 (43.8%) | 53 (34.2%)  | 0.210 | 59 (43.7%) | 0.088 | 0.084 |
| AG               | 73 (48.0%) | 90 (58.1%)  | 72 (53.3%) |
| GG               | 14 (9.2%)  | 12 (7.7%)   | 4 (3.0%) |
of rs2120243 differed significantly between the DN and the NDN groups \((p<0.05\), Table 2). We detected a lower risk of developing DN in individuals with the AA variant of rs2120243 (OR=0.213, 95% CI=0.055–0.826, \(p=0.025\), Table 3). In addition, the A allele appeared to decrease the susceptibility to DN (OR=0.688, 95% CI=0.476–0.994, \(p=0.046\), Table 3), which suggested that the A allele of rs2120243 may be a protective factor against DN in diabetic patients. Although the genotype and allele frequencies of rs1840680 did not differ significantly between the DN and NDN groups (\(p>0.05\), Table 2), we found that

Table 2 continued. The distributions of genotype and allele of PTX3 SNPs in patients with diabetic nephropathy (DN group), non-diabetic nephropathy (NDN group) and normal controls (NC group) (n/%).

| Genotypes/Allele | NC (n=152) | NDN (n=155) | P* | DN (n=135) | P# | P& |
|------------------|------------|-------------|----|------------|----|----|
| rs7616177 AA     | 203 (66.8%)| 196 (63.2%) | 0.356| 190 (70.4%)| 0.355| 0.069|
|                  |            |             |     | 114 (36.8%)| 80 (29.6%)|    |
|                  | G          | 101 (33.2%) |     |            |     |    |
|                  | GG         | 70 (46.1%)  | 0.057| 61 (45.2%)  | 0.028| 0.172|
|                  | GA         | 64 (42.1%)  |     | 86 (55.5%)  | 69 (51.1%)|    |
|                  | AA         | 18 (11.8%)  |     | 12 (7.7%)   | 5 (3.7%)|    |
|                  | G          | 204 (67.1%) | 0.499| 191 (70.7%) | 0.348| 0.111|
|                  | A          | 203 (66.8%) |     | 190 (70.4%)| 0.355| 0.069|

Table 3. Associations of PTX3 SNPs with the risk of diabetic nephropathy in type 2 diabetic patients.

| Genotypes/Allele | OR (95%CI) | P |
|------------------|------------|----|
| rs2305619 AA     | Ref.       |
|                  |            |    |
|                  | AG         | 3.411 (1.173–9.923) | 0.024|
|                  | GG         | 4.078 (1.370–12.135) | 0.012|
|                  | A          | Ref.       |
|                  | G          | 1.424 (0.993–2.041) | 0.054|
| rs2102243 CC     | Ref.       |
|                  | CA         | 0.706 (0.424–1.174) | 0.179|
|                  | AA         | 0.213 (0.055–0.826) | 0.025|
|                  | G          | Ref.       |
|                  | A          | 0.688 (0.476–0.994) | 0.046|
| rs1456099 TT     | Ref.       |
|                  | TA         | 1.447 (0.813–2.575) | 0.209|
|                  | AA         | 1.573 (0.786–3.147) | 0.201|
|                  | G          | Ref.       |
|                  | T          | 1.267 (0.897–1.789) | 0.179|
| rs7634847 GA     | Ref.       |
|                  | GA         | 0.812 (0.481–1.370) | 0.436|
|                  | AA         | 0.354 (0.065–1.917) | 0.228|
|                  | G          | Ref.       |
|                  | A          | 0.765 (0.495–1.183) | 0.228|

OR – odds ratio; 95%CI – 95% confidence intervals; Ref – reference. In the multivariate model, the following variables were added as independent variables: age, sex, history of hypertension, duration of diabetes and glycosylated hemoglobin.
AA homozygous individuals showed a lower risk of DN than GG homozygous individuals (OR=0.370, 95% CI=0.140–0.977, p=0.045, Table 3). Similarly, for rs2316706, no differences in genotype or allele frequency were observed between the DN and NDN groups (p>0.05, Table 2); however, the TT genotype exhibited a protective effect against DN (OR=0.345, 95% CI=0.132–0.903, p=0.030, Table 3). With respect to rs1456099, rs7634847, rs2316709, and rs7616177, no evidence of association with DN was found (all p>0.05, Tables 2, 3).

Haplotype analysis of PTX3 SNPs

We quantified the linkage disequilibrium (LD) between the two PTX3 SNPs found to show a significant association with DN. We also investigated whether certain PTX3 haplotypes, or combinations of alleles at different loci, were associated with an increased risk of DN. We identified one haplotype block in our population (Figure 1). We compared haplotype distributions between the DN and NDN groups, and observed that the CAGGG haplotype in block 1 was associated with DN (p=0.0319) (Table 4).

Associations between PTX3 and type 2 diabetes

As shown in Table 5, no difference in the allele frequencies of the eight SNPs was observed between the NC and T2DM groups (all p>0.05).

Discussion

PTX3 is synthesized in extrahepatic tissues and cells, including atherosclerotic lesions [20], adipose tissue [21], vascular endothelial cells, and macrophages [5]. A previous study in a mouse model showed that PTX3 is expressed in peritubular endothelial cells of the kidney [22]. In humans, expression of PTX3 is also observed in primary proximal renal tubular epithelial cells (PTECs), primary mesangial cells, and renal fibroblasts.
in kidney tissues [23,24]. Furthermore, increased plasma levels of PTX3 were observed in patients with CKD [11–13] and DN [12,14,25]. In addition, plasma PTX3 levels and urinary protein excretion can normalize though the treatment of the renin-angiotensin system, and/or with calcium channel blockers can normalize in patients with type 2 diabetes who show proteinuria [25,26]. All the aforementioned evidence suggests that abnormal PTX3 expression may contribute to renal damage.

Here, we provide evidence of the association between PTX3 variants and DN in a population of Han Chinese patients with type 2 diabetes. We found that variants of rs2305619 and rs2120243 in PTX3 were associated with susceptibility to DN in patients with diabetes. The SNPs rs2305619 and rs2120243 are located in the first intron and the 5’ promoter region of PTX3, respectively. These two SNPs may alter transcriptional regulation, resulting in abnormal splicing, or the transcriptional dynamics of the PTX3, as implied in previous studies that identified an association between rs2305619 and rs2120243 and plasma PTX3 levels [13–15]. It is equally possible that these two SNPs may be in linkage disequilibrium with other functional loci for development of DN in patients with diabetes. Further investigation is needed to clarify the role of these two SNPs in the pathogenesis of DN.

Although we identified a role of PTX3 in the pathogenesis of DN, the mechanism remains unclear. According to studies published to date, several mechanisms might be implicated in the process of renal function impairment in T2DM, including endothelial dysfunction and/or chronic low-grade inflammation. Endothelial dysfunction is an important contributor to the development of DN [27,28], as endothelial dysfunction influences mesangial cell and podocyte function and increases the permeability of glomerular basement membrane [27]. Indeed, PTX3 is known to be linked to endothelial dysfunction [29,30], and endothelial dysfunction has been reported to be ameliorated by suppression of PTX3 expression [31]. Given the strong links among PTX3, endothelial dysfunction, and DN, PTX3 may play a role in renal damage through endothelial dysfunction. In addition, inflammatory processes may be a main cause of endothelial dysfunction [32]. PTX3 is produced at sites of inflammation and regulated by stimulation with proinflammatory stimuli (IL-1β and TNF-α) [24] and via the activation of toll-like receptors (TLRs) [22], and via several pathways, including the PI3K/Akt axis and the NF-κB pathway [5]. Moreover, these proinflammatory cytokines and signaling pathways are also known to be crucial for development of DN [33]. On the basis of these findings, we speculate that PTX3 may act as an inflammatory mediator for the process of

| Allele | NC (n=152) | DM (n=290) | p     | OR (95%CI) | P     |
|--------|------------|------------|-------|------------|-------|
| rs2316709 | A          | 203 (66.8%) | 386 (66.6%) | 0.946 | Ref. |
|         | G          | 101 (33.2%) | 194 (33.4%) | 0.847 (0.449–1.596) | 0.607 |
| rs2305619 | A          | 111 (36.5%) | 208 (35.9%) | 0.848 | Ref. |
|         | G          | 119 (63.5%) | 372 (64.1%) | 1.216 (0.656–2.254) | 0.535 |
| rs2120243 | C          | 206 (67.8%) | 390 (67.2%) | 0.875 | Ref. |
|         | A          | 98 (32.2%) | 190 (32.8%) | 0.817 (0.429–1.556) | 0.539 |
| rs7616177 | G          | 204 (67.1%) | 391 (67.4%) | 0.926 | Ref. |
|         | A          | 100 (32.9%) | 189 (32.6) | 0.837 (0.445–1.572) | 0.580 |
| rs2316706 | T          | 101 (33.2%) | 199 (34.3%) | 0.919 (0.494–1.708) | 0.789 |
|         | G          | 241 (79.3%) | 465 (80.2%) | 0.752 | Ref. |
| rs7634847 | A          | 63 (20.7%) | 115 (19.8%) | 0.946 (0.670–1.335) | 0.752 |
| rs1456099 | T          | 153 (50.3%) | 309 (53.3%) | 0.405 | Ref. |
|         | A          | 151 (49.7%) | 271 (46.7%) | 1.002 (0.553–1.816) | 0.994 |
| rs1840680 | G          | 200 (65.8%) | 377 (65.0%) | 0.815 | Ref. |
|         | A          | 104 (34.2%) | 203 (35.0%) | 0.827 (0.441–1.549) | 0.552 |

NC – normal control; DM – type 2 diabetes; OR – odds ratio; 95%CI – 95% confidence intervals; Ref – reference. In the multivariate model, the following variables were added as independent variables: age, sex, history of hypertension, and glycosylated hemoglobin.
DN. We are interested in further investigation of the molecular mechanisms underlying the action of PTX3 in the development of DN.

Although plasma PTX3 level has previously been shown to be related to insulin resistance [34,35] and insulin secretion [21], we failed to detect a significant association between PTX3 polymorphisms and susceptibility to diabetes mellitus in this population.

Our study had several limitations. First, the sample size was relatively small, and only Chinese individuals were included, which limits the power of our results. Additionally, we did not measure plasma concentrations of PTX3 in these individuals. Thus, further studies in a larger, ethnically diverse population are necessary to elucidate the role of PTX3 in development of DN.

Conclusions

In conclusion, the present study found that certain variants of PTX3 predispose Han Chinese patients with type 2 diabetes to DN.

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Conflict of Interests

The authors state no conflicts of interests.
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