Association of PARL Gene Rs3732581, Rs73887537 Polymorphisms with Type 2 Diabetes Mellitus, Insulin Resistance and Blood Lipid Levels in Chinese Population

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Abstract

Aim: The aim of the current study was to investigate the associations between rs3732581, rs73887537 of PARL gene with type 2 diabetes mellitus and its related phenotypes in Chinese T2DM case-control population.

Methods: We genotyped PARL gene rs3732581, rs73887537 polymorphisms in 543 T2DM patients and 384 healthy controls by using PCR-RFLP technique. Plasma glucose, insulin and lipid were measured by biochemical technique.

Results: rs73887537 polymorphism of PARL gene was not existed in the studied population. The genotype and allele distributions of rs3732581 polymorphism were not significantly different between T2DM and control groups (both P>0.05). However compared with carriers of C allele, the carriers of the GG genotype showed significantly higher levels of triglyceride, total cholesterol in the T2DM and control groups respectively.

Conclusion: rs73887537 polymorphism of PARL gene was not existed in the Chinese studied population. The rs3732581 polymorphism of PARL gene is not associated with the presence of T2DM. However, it is associated with blood lipid levels in T2DM and healthy Chinese population differently.

Keywords: PARL gene; Type 2 diabetes mellitus; Insulin resistance; Blood lipid levels; Polymorphisms

Introduction

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder, caused by multiple environmental and genetic factors. A considerable amount of research has been devoted to defining the genes involved in the aetiology of this widespread disease. Impairment of mitochondrial function is intrinsically related with diabetes and alterations in mitochondrial function are associated with both insulin resistance and loss of energy-dependent beta-cell insulin secretion [1]. Thus proteins regulating mitochondrial action and efficiency have become attractive candidates for diabetes susceptibility in the face of adverse environmental risk factors [2].

The presenilins-associated rhomboid-like (PARL) protein is an inner mitochondrial membrane rhomboid protease. Given the likely role of PARL in maintaining mitochondrial membrane integrity and function, and the known defects of mitochondria in diabetes [3-8]. The association of PARL and insulin resistance had been investigated. Walder K et al. reported that both in human and in animal subjects PARL expression is negatively correlated with blood glucose and plasma insulin levels [9]. The expression of the PARL homologue is reduced by 50% in skeletal muscle of obese, type 2 diabetic Psammomys obesus relative to lean insulin sensitive animals. Exercise training, ameliorating symptoms of T2DM by reducing the plasma levels of glucose and insulin, also increased the levels of PARL in skeletal muscle [9]. Tang H et al. reported that the PARL mRNA level was lower in the insulin-resistant rats than in control animals, and is associated with low mitochondrial content and reduced mitochondrial enzyme activity in the skeletal muscle from the insulin-resistant rats [10]. These results suggest that high-fat-diet-induced insulin resistance is associated with mitochondrial dysfunction in skeletal muscle, and may be the result of the decreased expression of the PARL gene [9,10]. It has been shown that PARL is a new candidate gene for obesity and T2DM [9].

Walder et al. reported that a SNP variant (Leu262Val) in PARL (dbSNP ID rs3732581 mapped to chromosome 3q27, a region reportedly linked to phenotypes associated with metabolic syndrome) was associated with insulin resistance in an age dependent manner in an American-Caucasian case–control study [9,11]. They believed that variation in PARL sequence may be an important new risk factor for T2DM and other components of the metabolic syndrome [9]. However, subsequent replicated studies failed to replicate the initial findings and disputed the association between this polymorphism and two measures of insulin resistance (fasting plasma insulin and blood glucose levels) [12-14]. T2DM is likely to be polygenic and multiple factors common disease of which genetic heterogeneity exists in different race and areas. The populations were recruited in the previous study are always European descents. Until now it is unclear whether this polymorphism is associated with T2DM and its related phenotypes in the Chinese population and due to the previous conflicting association results, the aim of the current study was to investigate the relationship between the rs3732581, rs73887537 variants and T2DM and its related phenotypes including fasting plasma insulin, glucose levels and BMI et al in Chinese T2DM case–control population.

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Materials and Methods

Subjects

A total of 927 Northwest Han Chinese individuals aged between 22 and 88 years in Gansu was recruited into this case–control study, among them 543 unrelated type 2 diabetic patients were recruited from the inpatients who were admitted to Gansu Provincial People's Hospital in 2008 and 2009. 384 controls who were ethnically age- and gender-matched unrelated healthy volunteers were selected randomly during the same period in Medical Examination Center (MEC) of the People's Hospital of Gansu Province. Identification of T2DM was based on the World Health Organization Definition (WHO) 1999 definition [15]. The controls and the patients were matched by age and sex. All subjects had no family history of diabetes and no history of significant concomitant diseases. T1DM, acute or chronic hepatopathy and nephropathy, severe ethanol abuse, cigarette abuse were excluded by clinical and laboratory examination. All the participants gave written informed consent, and the Ethics Committee of Lanzhou University approved all research protocols.

Measurement

Full history and physical examination was taken. Venous blood sample of 5 ml was drawn from all subjects into tubes containing ethylene diamine tetraacetic acid after an overnight fast. Plasma glucose concentrations were measured by the glucose oxidase-peroxidase method. Serum levels of insulin were measured by radioimmunoassay method. Serum concentrations of lipids including total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and HbA1c were measured using standard methods in Clinical Laboratory in Gansu Provincial People's Hospital. Insulin resistance and pancreatic B-cell function were assessed by homeostasis model assessment (HOMA-IR) as fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5 [16]. Height (m) and weight (kg) were measured and body mass index was calculated as weight/height². Waist, hip circumferences (cm) were measured and waist/hip ratio and BMI were calculated. Anthropometric measurements from cases and control subjects were done in our ward in Medical Examination Center, respectively. The phenotypic characteristics of the study population are summarized in Table 1.

PCR amplification

Genomic DNA was extracted from peripheral blood leucocytes according to a standard protein K digestion and phenol/chloroform extraction method. Extracted DNA was dissolved in the appropriate volume of double distilled water. DNA concentration was measured with a nuclear acid analyzing instrument before preserving in -80°C. The reference sequence (i.e. wild type sequence) of PARL gene was extracted from the NCBI GenBank. We designed a set of primers using Primer 5.0 and Oligo 6.0 software to amplify a 1540-bp region that contains two single nucleotide polymorphism sites (rs3732581 and rs73887537 of PARL gene) by Polymerase Chain Reaction (PCR). The forward primer was 5'-ATAAGCCACCCACCCAGTT-3' , and the reverse primer was 5’-ACCACAAGGGCCAGAGTTAGA-3’. (Primers were synthesized by Shanghai Sangon Biological Engineering Technology And Service Co., Ltd.). PCR was performed in a 50µL volume containing 2U of Taq Plus DNA polymerase, 5 µl of 10×Buffer, 2 µl of dNTP Mixture each 10 mM solution, 40 pM of each primer, and appropriate volume of sterile water.

The PCR conditions were as follows. Initial denaturing was performed at 94.0°C for 5min, and was followed by 35 cycles of denaturing at 94.0°C for 35 s, annealing at 63.5°C for 30 s, extension at 72.0°C for 1 min10s, and final extension at 72.0°C for 7 min. The PCR products were separated by electrophoresis on 2.0% agarose gel. DNA Marker-D (100pb-2000bp); lane 1-6, Length of PCR production was 1540 bp; lane 7, negative control (no template DNA).

![Figure 1: Agarose gels electrophoresis after PCR. The amplified products were separated by electrophoresis on 2.0% agarose gel. DNA Marker-D (100bp-2000bp); lane 1-6, Length of PCR production was 1540 bp; lane 7, negative control (no template DNA).](Image 334x535 to 546x729)

Table 1: Baseline clinical characteristics of patients and controls. T± s

<table>
<thead>
<tr>
<th>Variable (units)</th>
<th>Controls</th>
<th>T2DM</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>384</td>
<td>543</td>
<td>0.627</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>213/171</td>
<td>279/264</td>
<td>0.219</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>55.75 ± 13.66</td>
<td>57.50 ± 11.80</td>
<td>0.230</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.68 ± 7.55</td>
<td>164.68 ± 7.47</td>
<td>0.252</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>68.46 ± 10.84</td>
<td>68.69 ± 12.49</td>
<td>0.866</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>24.86 ± 3.14</td>
<td>25.26 ± 3.93</td>
<td>0.277</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>86.31 ± 8.35</td>
<td>89.14 ± 9.01</td>
<td>0.005**</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>96.36 ± 9.52</td>
<td>94.94 ± 6.72</td>
<td>0.125</td>
</tr>
<tr>
<td>Waist and hips ratio</td>
<td>0.90 ± 0.07</td>
<td>0.94 ± 0.08</td>
<td>0.000**</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>4.63 ± 0.50</td>
<td>10.69 ± 4.19</td>
<td>0.000**</td>
</tr>
<tr>
<td>Fasting insulin (mU/L)</td>
<td>8.21 ± 2.47</td>
<td>10.24 ± 4.28</td>
<td>0.000**</td>
</tr>
<tr>
<td>Hemoglobin A1c (%)</td>
<td>4.62 ± 0.75</td>
<td>8.36 ± 1.83</td>
<td>0.000**</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.70 ± 0.59</td>
<td>4.87 ± 2.88</td>
<td>0.000**</td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>4.61 ± 0.67</td>
<td>4.83 ± 1.06</td>
<td>0.053</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.70 ± 0.79</td>
<td>2.19 ± 1.51</td>
<td>0.010*</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.41 ± 0.67</td>
<td>2.71 ± 0.97</td>
<td>0.003**</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.39 ± 0.30</td>
<td>1.07 ± 0.73</td>
<td>0.000**</td>
</tr>
</tbody>
</table>

Note: M: Male; F: Female; HOMA-IR: Homeostasis Model Assessment Insulin Resistance Index; TC: Total Cholesterol; TG: Triglyceride; LDL-C: High-Density Lipoprotein; HDL-C: Low-Density Lipoprotein; Sex Was Evaluated By Χ²-Test.∆: Mann-Whitney U Test Compared with Control. ∗P<0.05, ∗∗P<0.01

Figure 1: Agarose gels electrophoresis after PCR. The amplified products were separated by electrophoresis on 2.0% agarose gel. DNA Marker-D (100bp-2000bp); lane 1-6, Length of PCR production was 1540 bp; lane 7, negative control (no template DNA).
65°C for 20 min. The digested products were separated by 2% agarose gel electrophoresis and visualized by ethidium bromide staining. All samples were successfully genotyped and a random selection of samples underwent sequencing. There was no discordance noted between the RFLP-PCR assays and sequencing methods. For the PARL rs3732581 polymorphism (BstN I), GG homozygous cases were represented by DNA bands of 65, 219, 451, and 805 bp. CC homozygous cases were represented by DNA bands of 65, 219, and 1256 bp. CG heterozygous cases displayed a combination of both alleles (65, 219, 451, 805 and 125 bp). For the PARL rs73887537 polymorphism (Hpa II), TT homozygous cases were represented by DNA bands of 52, 391, 480, and 617 bp (Figure 2). CC homozygous cases were represented by DNA bands of 52, 391, 480, and 617 bp. TC heterozygous cases displayed a combination of both alleles (52, 272, 345, 391, 480 and 617 bp) (Figure 3).

**Results**

- Compared with the control subjects, T2DM patients had significantly higher waist circumference, Waist-to-Hip Ratio (WHR), Fasting Plasma Glucose (FPG), Fasting Insulin (FINS), Hemoglobin A1c (HBA1c), Insulin Resistance Index (HOMA-IR), the plasma levels of Triglyceride (TG), Low-Density Lipoprotein Cholesterol (LDL-C) and Lower High-Density Lipoprotein Cholesterol (HDL-C) (P<0.05). However, there were no significant differences in age, height, weight, hip circumference, Body Mass Index (BMI), and the plasma levels of Total Cholesterol (TC) between the two groups. This is consistent with diabetic features (Table 1).

- Genotyping of the PARL rs3732581 and rs73887537 variant was performed in 927 subjects, 543 with T2DM and 384 controls. We did not find rs73887537 polymorphism of PARL gene was existed in the studied Chinese population. PARL rs3732581 polymorphism genotype frequencies of GG, CG, and CC were 14.2%, 48.1%, 37.7% in T2DM group and 17.4%, 46.9%, 37.7% in control group respectively, and allele frequencies of G, C were 38.2%, 61.8% in T2DM group and 40.9%, 59.1% in control group respectively. Genotype frequencies did not deviate from Hardy–Weinberg equilibrium in the combined study population and no significant difference was observed in the allele or genotype frequencies of PARL gene rs3732581 polymorphism between the T2DM and control groups (both P<0.05). The distributions of PARL gene rs3732581 polymorphism genotypes and alleles in the T2DM and control groups from a Chinese population are summarized in Table 2.

- The subjects carrying GG genotype had higher plasma triglyceride level than that of the subjects carrying CG and CG+CC genotype (P<0.05) in T2DM group. The subjects carrying GG genotype had higher plasma triglyceride level than that of the subjects carrying CC and CG+CC genotype (P<0.05) and the subjects carrying GG genotype total cholesterol levels was higher than the subjects carrying CG and CG+CC genotype (P<0.05) in control group. Clinical characteristics by genotype are shown in Tables 3 and 4. However, there were no significant differences in other clinical characteristics in three genotypes in the two groups.

### Table 2: Genotype and allele distribution of the PARL Leu262Val polymorphism in case and control groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>N</th>
<th>Genotype frequency n (%)</th>
<th>Allele frequency n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GG</td>
<td>CG</td>
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<tr>
<td>T2DM</td>
<td>543</td>
<td>77 (14.2)</td>
<td>261 (48.1)</td>
</tr>
<tr>
<td>Control</td>
<td>384</td>
<td>67 (17.4)</td>
<td>180 (46.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>χ²</td>
<td>1.876</td>
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<tr>
<td>P value</td>
<td>0.391</td>
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*Statistical analysis*

Genotype and allele frequencies were calculated by gene counting. Tests of Hardy-Weinberg equilibrium were performed using χ² test. Clinical characteristics were expressed as mean ± SD. Comparisons of genotype and allele frequencies between T2DM group and controls were performed using χ² test. To compare the means of the variables measured between the groups, the Student’s t-test was used. One-way analysis of variance was used to test for differences in means of phenotypic characteristics between genotypes. For skewed distribution and homogeneity of variance the logarithmic transformation or nonparametric test was used. All P-values were two-tailed and Statistical significance was defined as P<0.05. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, Version 11.5) for Windows.

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Discussion

The present study demonstrated that distributions of the PARL rs3732581 genotypes and alleles are not statistically different between the T2DM and control groups in a Chinese population (P=0.391, 0.246 respectively). The results showed that the PARL rs3732581 variant is not association with the presence of T2DM in Chinese population, despite it has been shown that PARL appears to be one of the loci contributing to the chromosome 3 QTL cluster and a previous study reported a strong association of the genomic location of (3q27) with phenotypes typically associated with MetS [11,17-20]. But there have been no studies published further support the works showing that the PARL rs3732581 variant has no effect on these parameters in population-based cohorts [12-14]. The difference in results could be explained by race and/or environmental differences between the studied populations.

Our results on the genotype and allele distribution of the PARL rs3732581 variant in T2DM group of Chinese population were not similar to that reported for Irish population (P=0.002, 0.016 respectively). Allele distribution in control group of Chinese population was not similar to that reported for Australia population (P=0.044) [14]. The differences could due to race differences. In addition, we did not find rs73887537 polymorphism of PARL gene was existed in the studied Chinese population.

Interestingly, in this study it was noted that the subjects carrying G allele of rs3732581 had higher plasma triglyceride level than that of the subjects carrying C allele (P<0.05) in T2DM group. The subjects carrying C allele of rs3732581 variant in T2DM group of Chinese population were not similar to that reported for Irish population [11,17-20]. The different could due to race differences. In addition, we did not find rs73887537 polymorphism of PARL gene was existed in the studied Chinese population.
Mitochondria are highly dynamic organelles and undergo continuous fusion and fission events in physiological situations [22,23]. Mitochondrial structure and function are highly dependent on the processes of fusion and fission. PARL may involve in mitochondrial fusion [24]. Maintaining mitochondrial morphology is critical to normal cell function [25-33]. The imbalance in mitochondrial fusion and fission in metabolically active tissue such as skeletal muscle may result in defects associated with lipid metabolism [24]. There is substantial evidence that proteins participating in mitochondrial fusion or fission also have a role in metabolism [34-36]. Their expression is crucial in mitochondrial metabolism through the maintenance of the mitochondrial network architecture, and their reduced expression may explain some of the metabolic alterations associated with obesity. Kita et al. investigated the role of mitochondrial remodeling on Triacylglycerol (TG) accumulation in adipocytes and found that when the mitochondrial fusion was induced in adipocytes by silencing of mitochondrial fusion proteins including Fis1 and Drp1, the cellular TG content was decreased [37]. In contrast, the silencing of mitochondrial fusion proteins including mitofusin 2 and Opal1 increased the cellular TG content followed by fragmentation of mitochondria [37]. They also found that Polyphenolic phytochemicals, negative regulators of cellular TG accumulation in adipocytes, have mitochondrial fusion activity [37]. These results strongly suggest that cellular TG accumulation is regulated, at least in part, via mitochondrial fusion and fission processes. On the other hand, it has been shown that deletion of PARL in the mouse resulted in premature postnatal death due to progressive cachexia and indications of increased apoptosis which correlated with reduced levels of cleaved Opal1. The antiapoptotic effects of Opal1 require PARL [38-40]. PARL positioned upstream of Opal1 in the control of apoptosis [38]. Opal1 has been shown to be involved in the regulation of the so-called "cristae remodeling" pathway of apoptosis and the regulation of mitochondrial fusion [38,39,41]. Cipolat et al. provide evidence that PARL may be required for the correct assembly of the Opal1-containing structures that regulate the integrity of the cristae junctions and that PARL and Opal1 interacted at the protein level as well [38]. So it is tempting to speculate that the PARL rs3732581 genetic variant could in some way influence the mitochondrial remodeling and metabolism of lipid through its interaction with Opal1 [38,42].

Moreover, it is also well known that nuclear genome has a leading role in the biogenesis of mitochondrial respiratory chain and that nuclear activity can be modulated by signals sent by mitochondria suggesting that dysregulated mitochondrial morphology could alter gene expression of proteins involved in lipid metabolism [43-45]. PARL is the only intramembrane-cleaving protease where the putative signaling moiety is also part of the protease itself. The β-cleavage of PARL releases within the mitochondrial matrix a 25 amino acid long peptide termed β-P peptide which appears to execute mitochondrial retrograde signaling (MRS) [46-48]. MRS senses mitochondrial activities/dysfunctions and relay this information to the nucleus in order to initiate appropriate physiological readjustments including metabolism [48]. Indeed, the release of the β-P peptide, the putative effectors molecule of the PARL signaling, is self-regulated. The β-cleavage is either executed by an unknown protease (PARLase) that is activated via a PARL-catalyzed cleavage or by PARL itself through an intermolecular reaction [46]. The proteolytic activity of PARL required for the β-cleavage of its N terminus could be supplied in trans [46]. So, it is tempting to speculate that the PARL rs3732581 genetic variant could in some way influence the MRS and metabolism of lipid through alter the conformation of the protein and its proteolytic activity.

It has been suggested that mitochondria ensure metabolite and mitochondrial DNA mixing and impaired fusion could result in lower mitochondrial content and impaired oxidative capacity, leading to a defective energy homeostasis. Given the prior evidence for a role for PARL in mitochondrial integrity and function, multivariate analysis was performed to assess the global effect of PARL sequence variation on mitochondrial content. The results showing that sequence variation in PARL have a significant influence on mitochondrial content ($P=0.00076$). But the association between the PARL rs3732581 variant and mitochondrial content level is not significant ($P=0.0701$) [49]. The PARL rs3732581 variant alone is unlikely to significantly influence metabolism of lipid through alter the mitochondrial content.

In summary, until now the role of PARL and/or the PARL rs3732581 genetic variant on metabolism of lipid is poorly understood. The mechanism of regulation of plasma triglyceride and total cholesterol levels by PARL and/or the PARL rs3732581 genetic variant remains to be determined. The different effects of the PARL rs3732581 genetic variant on plasma triglyceride and total cholesterol levels between the T2DM and control groups, suggesting that there might exist differences in the biological pathways of the two phenotypes between the case and control groups and further studies are required, although we cannot rule out the possibility that one or more of our results represent false positive findings. In conclusion, we did not find the rs73887537 polymorphism of PARL gene was existed in studied Chinese population and our results provided no evidence that the PARL rs3732581 variant had a role in T2DM susceptibility or was likely to be an important contributor to insulin resistance in Chinese population. However, we found that compared with carriers of C-allele the carriers of the GG genotype showed significantly higher levels of triglyceride and levels of triglyceride and total cholesterol in the T2DM and control groups respectively. The PARL rs3732581 variant may play a role in genetic predisposition to dyslipidemia which is a risk factor of diabetes in Chinese population. Our original findings were required to replicate in additional populations. A role for rs3732581 polymorphism of PARL gene in metabolic conditions could not be excluded and further comprehensive studies are required.

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Reference


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