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The Uyghur population and genetic susceptibility to type 2 diabetes: potential role for variants in CAPN10, APM1 and FUT6 genes

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Abstract

Genome-wide association studies have successfully identified over 70 loci associated with the risk of type 2 diabetes mellitus (T2DM) in multiple populations of European ancestry. However, the risk attributable to an individual variant is modest and does not yet provide convincing evidence for clinical utility. Association between these established genetic variants and T2DM in general populations is hitherto understudied in the isolated populations, such as the Uyghurs, resident in Hetian, far southern Xinjiang Uyghur Autonomous Region, China. In this case-control study, we genotyped 13 single-nucleotide polymorphisms (SNPs) at 10 genes associated with diabetes in 130 cases with T2DM and 135 healthy controls of Uyghur, a Chinese minority ethnic group. Three of the 13 SNPs demonstrated significant association with T2DM in the Uyghur population. There were significant differences between the T2DM patients and controls in the risk allele distributions of rs3792267 (CAPN10) (P = 0.002), rs1501299 (APM1) (P = 0.017), and rs3760776 (FUT6) (P = 0.031). Allelic carriers of rs3792267-A, rs1501299-T, and rs3760776-T had a 2.24-fold [OR (95% CI): 1.35–3.71], 0.59-fold [OR (95% CI): 0.39–0.91], 0.57-fold [OR (95% CI): 0.34–0.95] increased risk for T2DM respectively. We further confirmed that the cumulative risk allelic scores calculated from the 13 susceptibility loci for T2DM differed significantly between the T2DM patients and controls (P = 0.001), and the effect of obesity/overweight on T2DM was only observed in the subjects with a combined risk allelic score under a value of 17. This study observed that the SNPs rs3792267 in CAPN10, rs1501299 in APM1, and rs3760776 in FUT6 might serve as potential susceptible biomarkers for T2DM in Uyghurs. The cumulative risk allelic scores of multiple loci with modest individual effects are also significant risk factors in Uyghurs for T2DM, particularly among non-obese individuals. This is the first investigation having observed/found genetic variations on genetic loci functionally linked with glycosylation associated with the risk of T2DM in a Uyghur population.

Keywords: type 2 diabetes ● susceptibility loci ● CAPN10 ● APM1 ● FUT6 ● Uyghur

Introduction

As a common heterogeneous disease, type 2 diabetes mellitus (T2DM) has become a global health catastrophe threatening economies especially in those of low- and middle-income countries in which more than 80% of diabetes deaths occur [1]. It is estimated that the number of people with diabetes worldwide will rise to 552 million in the year of 2030 if no urgent action is taken, and meanwhile diabetes will be the 7th leading cause of death [2, 3]. In China, 9.7% of Chinese adults are suffering from T2DM, 60.7% of them are unaware, and 15.5% have pre-diabetes at risk of cardiovascular diseases [4]. T2DM is characterized by two fundamental features: insulin resistance and progressive pancreatic β-cell dysfunction, corresponding defects in both insulin action and secretion respectively [5]. For the time being, ample evidence suggests that T2DM origins with an interaction between genetic (i.e., family history of diabetes) and environmental determinants (i.e., low physical exercise, smoking, high fat intake). Subsequent association studies on the role of genetic variants to predict T2DM in certain ethnic groups have produced conflicting results.
[6–10]. Thereby, it is imperative to explore and define population-specific genetic and environmental risk factors, which will shed light on the pathogenesis of T2DM.

Recently, the research of glycomics is becoming an important focus in different fields of biology and medicine. N-linked oligosaccharides of glycoproteins (N-glycans) based on individual background variability and inherent sensitivity reflect the integrative effect of both genetic and environmental factors on the individuals, so as to make N-glycans promising disease biomarkers [11–14]. Italian National Research Center has proved the application of serum N-glycan profiles, especially those of fucose-containing glycans, as sensitive surrogate biomarker for the presence of diabetes and metabolic syndrome [15]. Currently, except one report on N-Glycan profiling of metabolic syndrome in Chinese Han population [16], there is no study to link N-glycan profiles with these factors with diabetes from Chinese ethnic minorities. Thereby, there might be differences in the contribution of known single-nucleotide polymorphisms (SNPs) associated with fucosylation among various ethnic populations [17, 18].

In history, Xinjiang, in the northwestern frontier area of China, served as the key controlling section of the well-known Silk Road, which was an ancient network of trade and cultural transmission routes that were central to cultural interaction through regions of the Asian continent connecting the West and East by merchants, pilgrims, monks, soldiers, nomads, and urban dwellers from China and India to the Mediterranean Sea during various periods of time [19]. Consequently, the ethnic minorities including Uyghurs in Xinjiang became admixed populations with both eastern and western Eurasian ancestors [20]. However, as time goes on, the Uyghurs, living in Hetian, far southern Xinjiang Uyghur Autonomous Region, have been practicing consanguinity and endogamy since they settled down in the area some 2000–2500 years (80–100 generations) ago, and are highly distinguishable from both current Europeans and East Asians due to the endogamy and genetic isolation in terms of the time scale of historical events [20, 21]. Therefore, the Uyghurs are a classically well-defined isolated population, practicing endogamy resident in a relatively homogeneous environment and have large sib ships. And they are overwhelmingly Muslim, and have their own language, religious beliefs, and lifestyles that are very different from either Han Chinese population or American/European populations [18, 22].

In the previous pilot study, we found that 16 T2DM-related SNPs are of high level of variability and significant ethnic-specific differences in Uyghur population compared with the other ethnic groups [18]. This study aimed to further explore the possible association between 13 SNPs susceptibility loci and T2DM as well as the combined effects of these loci on the susceptibility of T2DM in a Uyghur population.

Materials and methods

Study participants

Between April 2012 and July 2013, we recruited a total of 265 Uyghur participants (130 T2DM patients and 135 healthy controls) from Hetian of Xinjiang, China, where the Uyghur population was less affected by the recent migration of Han Chinese. Both recruited cases and controls were not directly biologically related, and in addition they had no intermarriage history with other ethnic groups within the latest three generations. All subjects underwent routine health check-ups at local Minfeng Rennin Hospital in Hetian. Diagnosis of T2DM was made by physicians according to 1999 World Health Organization (WHO) Criteria (fasting plasma glucose greater than or equal to 7.0 mmol/l and/or 2-hrs plasma glucose greater than or equal to 11.1 mmol/l) [23]. Biochemical [fasting blood glucose (FBG), serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL)] and anthropometric measurements [height, weight, body mass index (BMI)] were conducted as earlier described [18]. Blood pressure was measured with a standard mercury sphygmomanometer in a sitting position after at least a 5 min. rest. Peripheral blood samples for analyses of biochemical indexes were collected in ethylenediaminetetraacetic acid anti-coagulated tubes after an overnight fast. The concentration of FBG was determined by the glucose oxidase-peroxidase method using commercial kits. Total cholesterol levels were analysed using cholesterol oxidase peroxidase-aminopyrine method, TG by glycerol phosphate oxidase amidopyrine method, HDL and LDL by enzymatic methods on a Hitachi 911 automated analyzer (Boehringer Mannheim, Mannheim, Germany).

All of the participants signed the informed consent before participation. This study was approved by the Ethical Committees of Xinjiang University, Urumqi, China and Capital Medical University, Beijing, China.

Selection of the candidate SNPs

Thirteen SNPs [rs7754840 (CDKAL1), rs13266634 (SLC30A8), rs4402960 (IGF2BP2), rs1501299 (APM1), rs2237892 (KCNQ1), rs2237895 (KCNQ1), rs35767 (IGF1), rs3792267 (CAPN10), rs10483776 (FUT8), rs7159888 (FUT8), rs3760776 (FUT6), and rs7953249 (HNF13)] were selected for the following reasons. Firstly, we analysed nine SNPs from seven genes that had a nominal to strong association with T2DM identified by genome-wide association studies (GWAS) among populations of European or Asian ancestry, i.e., APM1, IGF1, CDKAL1, IGF2BP2, SLC30A8, KCNQ1, and CAPN10 [24]. CAPN10 gene has been identified as the first genetic locus susceptible to T2DM by positional cloning in Finland [25]. In addition, four SNPs [rs10483776 (FUT8), rs7159888 (FUT8), rs3760776 (FUT6), and rs7953249 (HNF13)] were selected based on their associations with plasma fucosylation status [26]. Although more and more susceptibility loci for T2DM are being identified, such glycosylation linked foundational loci have not yet been examined up to date. Minor allele frequencies (MAF) of all selected SNPs are more than 0.05 in both HapMap CEU data and HapMap CHB data (http://hapmap.ncbi.nlm.nih.gov/).

SNPs genotyping

Genomic DNA was isolated from 200 μl venous blood samples using QIAamp DNA Blood Mini Kit according to the manual instructions (Qiagen Inc., Hilden, Germany). The concentration and purity of the isolated DNA were measured using the Thermo Scientific NanoDrop 2000 spectrophotometer according to the manufacturer. The DNA samples were genotyped by using Sequenom MassARRAY iPLEX Platform (Sequenom Inc., San Diego, CA, USA) [18]. The PCR was executed in a 5 μl volume containing 1.8 μl deionized H2O, 0.5 μl 10× PCR buffer, 0.4 μl 25 mM MgCl2,
Inc.) using MassARRAY reaction products were spotted onto a SpectroCHIP array (Sequenom molecular grade water and 6 mg clean resin (Sequenom Inc.) was added of distribution of all continuous variables was verified using the Kol–

ergy was performed and results were visualized on the MassARRAY matrix-assisted laser desorption/ionization time-of-flight mass spectrom-

squared test. (HWE) for genotype frequencies was tested in both groups using chi-

Rtest or rank sum test –test or rank sum test

Statistical analysis

All continuous variables were expressed as the mean ± S.D. Normality of distribution of all continuous variables was verified using the Kol-

mogorov-Smirnov tests. Continuous variables between T2DM and control groups were compared by Student’s t-test or rank sum test according to the results of Normality tests. Hardy-Weinberg equilibrium (HWE) for genotype frequencies was tested in both groups using chi-

quared test. $P \geq 0.05$ was considered to obey the HWE. We consid-

erated the dominant and recessive genetic models in which the genotype was assigned as 0 or 1, depending on whether subjects carried the minor allele (genotype 1 for minor allele carrier, 0 for not, under domi-

nant model; genotype 1 for homozygous for minor allele, 0 for not, under recessive model) [27]. Allelic frequencies in T2DM patients and controls were compared by chi-squared test, and logistic regression analyses were applied to evaluate differences in genotype distributions. Odds ratios (ORs) were calculated after adjustment for age, gender and BMI. In addition, to evaluate the combined effects of the SNPs, the cumulative risk allelic scores were calculated, based on the results of association analysis of candidate SNPs for T2DM. In such cases, we considered an additive genetic model for each SNP, and assigned a score of 0, 1, or 2 to the genotypes for the 13 loci, depending on whether subjects carried the wild-type allele or were heterozygous or homozygous for the risk allele [18]. The count method assumed that each risk allele contributes equally and independently to the risk for T2DM. The scores were modelled as a continuous variable and categorized into quartiles. The effects of cumulative risk allelic scores, obesity/overweight, and the interaction between the cumulative number of risk alleles and obesity/overweight on the risk of T2DM were tested using multivariate logistic regression. A two-sided $P < 0.05$ was considered statistically significant.

The statistical analysis was conducted using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Power calculations were performed under current sample size and MAF observed in this study using Quanto software version 1.2.4 (http://hydra.usc.edu/gxe).

Results

Sample characteristics

The demographic and clinical profiles of 265 Uyghur participants (130 T2DM patients versus 135 healthy controls) are presented in Table 1. The T2DM patients had significantly higher levels of BMI, SBP, DBP, TC, TG, LDL and FBG compared to the controls ($P < 0.05$). Significant difference was found neither in gender, nor in HDL between T2DM and healthy controls.
Table 1 Demographic characteristics and biochemical measures of the study participants

<table>
<thead>
<tr>
<th></th>
<th>T2DM (n = 130)</th>
<th>Control (n = 135)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.60 ± 11.15</td>
<td>56.36 ± 16.81</td>
<td>0.200</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>59 (45.4%)</td>
<td>52 (38.5%)</td>
<td>0.258</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.49 ± 3.51</td>
<td>24.08 ± 3.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>134.19 ± 18.54</td>
<td>120.41 ± 13.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>90.50 ± 13.42</td>
<td>80.42 ± 9.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC (mmol/l)</td>
<td>4.99 ± 0.99</td>
<td>4.01 ± 1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>1.88 ± 0.87</td>
<td>1.53 ± 0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.24 ± 0.30</td>
<td>1.24 ± 0.27</td>
<td>0.979</td>
</tr>
<tr>
<td>LDL (mmol/l)</td>
<td>2.83 ± 0.90</td>
<td>2.38 ± 0.76</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG (mmol/l)</td>
<td>8.78 ± 2.42</td>
<td>5.33 ± 0.66</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean ± S.D. The P-values with statistical significance are indicated in bold numbers. SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: Total cholesterol; TG: Triglycerides; BMI: body mass index; FBG: fasting blood glucose.

Fig. 1 Matrix-assisted laser desorption/ionization time-of-flight single-nucleotide polymorphism mass spectrum and call cluster plot.
SNPs rs1501299/GG and rs3760776/CC were more frequent in the T2DM group compared to the controls (63.1% versus 80%; 65.4% versus 51.1%; 78.5% versus 69.6%, respectively; Table 3).

To evaluate the combined effects of these 13 associated variants, we calculated the cumulative risk allelic scores of these 13 risk alleles that each participant had using a simple count approach. The average risk allele frequency for the subjects in the Q3 and Q4 groups (Table 4).

### Discussion

Genome-wide association studies have successfully identified over 70 loci associated with the risk of T2DM in multiple populations, especially in populations of European ancestry [28]. However, the risk attributable to an individual variant to date is modest and does not yet provide convincing evidence for clinical utility. Genetic studies have revealed that different populations have different genetic structures because of their complex demographic histories [29]. In addition, the heterogeneity of drug responses further illustrates the genetic variants vary substantially among different Chinese ethnic groups [22]. Therefore, current available data are not likely to be applicable to all populations. Uyghur is a classically well-defined isolated population, practicing endogamy resident in a relatively homogeneous environment and having large sibships. Therefore, it would be an ideal population for the study of genetic susceptibility.

### Study findings

In this population-based case-control study, we extended the support for T2DM candidate loci identified by GWAS [24] and revealed that
Table 3 Frequencies of the genotypes of rs3792267 (CAPN10), rs1501299 (APM1) and rs3760776 (FUT6) in T2DM patients and controls

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>T2DM no. (%)</th>
<th>Control no. (%)</th>
<th>P*</th>
<th>Logistic regression analysis (adjusted for age, gender and BMI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dominant</td>
<td>Recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>OR (95% CI)</td>
<td>P</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>rs3792267 (CAPN10)</td>
<td>GG</td>
<td>82 (63.1%)</td>
<td>108 (80%)</td>
<td>0.006</td>
<td>2.51 (1.42–4.46)</td>
</tr>
<tr>
<td></td>
<td>GA</td>
<td>42 (32.3%)</td>
<td>25 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>5 (3.8%)</td>
<td>2 (1.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs1501299 (APM1)</td>
<td>GG</td>
<td>85 (65.4)</td>
<td>69 (51.1)</td>
<td>0.034</td>
<td>0.51 (0.31–0.85)</td>
</tr>
<tr>
<td></td>
<td>GT</td>
<td>39 (30)</td>
<td>56 (41.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>5 (3.8)</td>
<td>8 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3760776 (FUT6)</td>
<td>CC</td>
<td>102 (78.5)</td>
<td>94 (69.6)</td>
<td>0.113</td>
<td>0.56 (0.31–0.99)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>26 (20)</td>
<td>36 (26.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TT</td>
<td>2 (1.5)</td>
<td>5 (3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The P-values for comparison of statistically difference among the three genotypes for certain SNP between T2DM and control subjects. † The logistic regression model was used to obtain the odds ratios of the minor allele with the major allele as reference group. The P-values with statistical significance are indicated in bold numbers.

Table 4 Effect of obesity/overweight on T2DM according to quartiles of risk allelic scores

<table>
<thead>
<tr>
<th>Quartiles of risk alleles</th>
<th>T2DM (n = 130)</th>
<th>Control (n = 135)</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subject</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>82</td>
<td>62</td>
<td>2.075</td>
<td>1.263–3.407</td>
<td>0.004</td>
</tr>
<tr>
<td>Non-obese</td>
<td>48</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (≤14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>28</td>
<td>33</td>
<td>2.158</td>
<td>1.002–4.647</td>
<td>0.049</td>
</tr>
<tr>
<td>Non-obese</td>
<td>19</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (15, 16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>32</td>
<td>18</td>
<td>2.431</td>
<td>1.022–5.782</td>
<td>0.044</td>
</tr>
<tr>
<td>Non-obese</td>
<td>16</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (17, 18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>18</td>
<td>10</td>
<td>0.667</td>
<td>0.150–2.973</td>
<td>0.595</td>
</tr>
<tr>
<td>Non-obese</td>
<td>9</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (≥19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>4</td>
<td>1</td>
<td>4.978</td>
<td>0.306–81.083</td>
<td>0.26</td>
</tr>
<tr>
<td>Non-obese</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* ORs and P-values on T2DM for obese/overweight and non-obese subjects were adjusted for age. The P-values with statistical significance are indicated in bold numbers.
the cumulative risk allelic scores that aggregate information from multiple genetic variants are significant risk factors in the Uyghur population. Among the 13 T2DM genetic susceptibility loci screened, we found significant association with T2DM for three of them, i.e., rs3792267 (CAPN10), rs1501299 (APM1) and rs3760776 (FUT6). CAPN10 gene, identified as the first susceptibility gene for T2DM by positional cloning [25], has been associated the increased risk of T2DM in different populations [30–32]. It has been well documented that the abnormal expression of CAPN10 in pancreatic islets, muscle and liver is related to insulin secretion and action, and thereby is considered to be an important novel pathway involved in glucose metabolism [25]. Single-nucleotide polymorphism rs3792267 polymorphism in CAPN10 has been examined on the effect of regulating insulin sensitivity and CAPN10 mRNA levels [33]. However, divergent results were reported and gave a heterogeneous picture owing to racial or regional differences [31, 32, 34, 35]. Our study revealed that the A allele of rs3792267 of CAPN10 was significantly associated with T2DM in Uyghur participants (P = 0.002, adjusted for age, gender and BMI) (Table 2).

A significant association was detected between the A allele of rs3792267 (CAPN10) and T2DM susceptibility in the dominant model (P = 0.002; Table 3). Kommoju et al. showed that the increased A allelic frequency of rs3792267 in the T2DM patients than that of controls in a Indian population of Hyderabad [36], conferring the risk for developing T2DM. Another study conducted on the Kurdish ethnic group of Iran population also supported the association of A-allele of rs3792267 with T2DM [10], which was consistent with the results of this study for Uyghur participants. Furthermore, Li et al. also reported association of the A allele with high risk of T2DM in Uyghur population [6]. Yet, some studies showed two opposite trends of statistical significance of the G- and A-allele towards T2DM in certain population [34]. This discrepancy suggested that the association should be population-specific due to the differential allelic frequencies across different ethnic human groups. The distribution of the ancestral G allele at rs3792267 in controls reported in previous studies varied from 0.68 to 0.97 in different populations such as European [25, 37, 38], Arabic [39], African-American [40], South Indian [41], Japanese [42] and Chinese [43]. The frequency of the G allele for rs3792267 in Uyghur controls (0.893) was reported to be similar level with African-Americans, Tunisian Arab and South Indian, but higher than that in Caucasian populations from Britain and Ireland, and lower than that in Japanese. Uyghur, as one of typical Muslim minorities [44], has high levels of consanguineous and/or endogamous marriage which might increase the likelihood of presence of pathogenic mutations at a higher homozygous level, with mean inbreeding coefficient of 0.0033–0.0065 [45]. Therefore, the accumulation of various mutations due to endogamy seems to affect the distribution of allele frequency across different population groups [18, 46, 47].

Among the other loci examined in this study, SNP rs1501299 in APM1 also showed the significant association with T2DM in Uyghur participants (P = 0.017, adjusted for age, gender and BMI, Table 2). Single-nucleotide polymorphism rs1501299 locates in intron-2 within the APM1 gene, which plays a pivotal role in regulating insulin sensitivity [48]. In this case–control study, the frequency of GG genotype of rs1501299 was noted significantly higher in T2DM patients as compared with that of controls, suggesting that the G allele may confer increased risk for T2DM. Indeed, a significant association was detected between the G allele of rs1501299 and T2DM susceptibility in the dominant model (Table 3). Tu et al. reported that the rs1501299 polymorphism was associated with increased risk for T2DM, especially in Chinese Han population [49]. The direction and magnitude of our result were consistent with these previous reports [50, 51].

FUT6 gene, as a member of fucosyltransferase (FUT) family, is involved in catalysing the inverting reaction, in which a fucose residue is transferred from guanosine-diphosphate fucose (GDP-Fuc) to molecules such as N-glycans [52]. Single-nucleotide polymorphism rs3760776, in the promoter region of FUT6 [53], was also reported to have association with plasma levels of fucosylated glycans such as DG7 (P = 3.42 × 10-15) and DG9 (P = 3.51 × 10-15) [26]. In mammals, fucose-containing glycans have been shown to be associated with the host-microbe interactions, transfusion reaction and selectin-mediated leucocyte-endothelial adhesion [54, 55]. In our case–control study, the frequency for the T allele in rs3760776 was noted significantly lower in diabetic patients as compared with that of controls (P = 0.031). In logistic regression analysis, marginal association for SNP rs3760776 was detected in dominant model (OR = 0.56, 95% CI: 0.31–0.99, P = 0.049) (Table 3). Single-nucleotide polymorphism rs3760776 may affect the activity of FUT6 enzyme, and thus may alter individual's capacity to fucose conversion and in turn modify the risk in the development of T2DM. The study on the glycosylation profiling of this same cohort of Uyghur T2DM patients is currently under way in our laboratory to understand the molecular mechanism underlying the statistically significant associations observed in this study.

Although significantly associated with T2DM, the risk attributable to an individual variant is modest, which limits the clinical utility. However, taken collectively, a combination of information from multiple genetic variants may contribute substantially to the disease risk and will be useful in characterizing population at high risk for T2DM. We have shown that the cumulative risk allelic scores based on the 13 susceptible loci for T2DM are significant risk factors in the Uyghur population samples (P = 0.001), consistent with several previous studies in Asian populations [18, 56, 57]. In addition, our data suggested that obesity/overweight is a strong predictor of T2DM (P = 0.004), given obesity is associated with insulin resistance [58]. However, obesity/overweight was not shown as a significant risk factor of T2DM for the patients with the combined risk allelic scores greater than or equal to the value of 17; perhaps due to the small sample size in the subgroups, such as Q3 and Q4, with insufficient statistical power. This result was comparable with the study among a Japanese population [59], in which most T2DM patients were characterized by a low BMI and shared the same pattern of genetic profiling on the T2DM susceptible loci.

Study limitations

Our study has limitations. A relatively small sample size: the blood sampling of minority groups was a very hard field-practice in the remote areas of Xinjiang [18, 22]. Thereby, the combined data set
provided statistical power of less than 80% (40.9–64.7%) to detect SNPs with risk ratios greater than 1.5, given the significance level of 0.05. Thus, case-control studies with large samples and multiple comparisons are required to confirm the effect of those SNPs on the T2DM risk based on this current observation. Moreover, GWAS identify SNPs and other DNA variants associated with a disease, but cannot on their own specify which genes are causal [60, 61]. Thereby, function studies in carefully selected study participants and animal model are also needed to specify the molecular mechanism underlying the statistical association observed.

Conclusion

The SNP rs3792267 in CAPN10, rs1501299 in APM1, and rs3760776 in FUT6 might serve as potential susceptibility loci for T2DM in Uyghurs. The cumulative risk allelic scores of multiple loci with modest individual effects are also significant risk predictors/factors in Uyghurs for T2DM, particularly among non-obese individuals. This is the first investigation having observed/found genetic variations on genetic loci functionally linked with glycosylation associated with the risk of T2DM in a Uyghur population.

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Conflict of interest

None.

Author contribution

WW and MSS designed the study, wrote and revised the manuscript. FFZ performed the analysis and interpretation of data, and draft the manuscript. MD contributed to acquisition of data (population studies) and reviewed the manuscript. YXW contributed to acquisition of data (genetics) and reviewed the manuscript. HXF, HW, QG, HD, SGQ, XYY, JZ and LJW provided technical support for the analysis and interpretation of data, and critical revision of the manuscript. All authors read and approved the final manuscript.

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