Genetic variation in Tanis was associated with elevating plasma triglyceride level in Chinese nondiabetic subjects

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Abstract

Background: The association of genetic polymorphisms of Tanis with triglyceride concentration in human has not been thoroughly examined. We aimed to investigate the relationship between triglyceride concentrations and Tanis genetic polymorphisms.

Methods: All participants (n=1497) selected from subjects participating in the Cardiovascular Risk Survey (CRS) study were divided into two groups according to ethnicity (Han: n=1059; Uygur: n= 438). Four tagging SNPs (rs12910524, rs1384565, rs2101171, rs4965814) of Tanis gene were genotyped using TaqMan® assays from Applied Biosystems following the manufacturer's suggestions and analyzed in an ABI 7900HT Fast Real-Time PCR System.

Results: We found that the SNP rs12910524 was associated with triglyceride levels by analyses of a dominant model (P<0.001), recessive model (P < 0.001) and additive model (P < 0.001) not only in Han ethnic but also in Uygur ethnic group, and the difference remained significant after the adjustment of sex, age, alcohol intake, smoking, BMI and plasma glucose (GLU) level (All P < 0.001). However, this relationship was not observed in rs1384565, rs2101171, and rs4965814 before and after multivariate adjustment (All P > 0.05). Furthermore, there were significant interactions between rs12910524 and GLU on TG both in Han (P=0.001) and Uygur population (P=2.60×10⁻⁹).

Conclusion: Our results indicated that the rs12910524 in the Tanis gene was associated with triglyceride concentrations in subjects without diabetes in China.

Keywords: Genetics, Tanis, Triglyceride, Diabetes, Polymorphisms

Background

Elevating triglycerides (TG) level, an essential component of the metabolic syndrome, is independently associated with coronary artery disease (CAD) [1]. High levels of fasting plasma TG are caused by not only environmental factors such as smoking[2-4], high-fat diet and alcohol intake [5,6], but also genetic factors including single nucleotide polymorphisms (SNPs). However, till date, only several candidate genes involving lipid metabolism [7-10] and CAD [11-14] have been discovered, and these genes only explain a small fraction of the total interindividual variation in plasma TG levels [15-17].

Tanis, a novel discovered membrane protein, has been suggested to be involved in the development of diabetes and dyslipidemia [18,19]. In a polygenic animal model of type 2 diabetes model-Psammomys obesus, the Tanis was found to be positively correlated to circulating TG concentrations [19]. However, the association of genetic polymorphisms of Tanis with plasma TG concentration in humans has not been thoroughly examined. In addition, Tanis was identified as a newly found receptor of amyloid A-1 (SAA1), which is not only an inflammatory marker but also an apolipoprotein [20]. In the previous study [20,21], we found that SAA1 gene polymorphisms were associated with dyslipidemia in Chinese subjects. Tanis, as...
a receptor of SAA1, also called SELS, located on chromosome15q26.3, encodes selenoprotein S which participates in the retro-translocation of misfolded proteins from the endoplasmic reticulum (ER) to the cytosol for their degradation [22]. Several previous studies indicated that the variations in Tanis gene were associated with pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β and TNF-α [23] and cardiovascular disease [24] and metabolic factors [25]. However, the relationships between Tanis gene and lipid profile have not been thoroughly investigated. Xinjiang is part of the ancient Silk Road and borders eight countries including Russia, Kazakhstan, Kirghizastan, Tajikistan, Pakistan, Mongolia, India, and Afghanistan. There are more than 13 ethnic groups living in this area. Among them, the Uygur people account for 46%, and Han account for 40%. In this study, we aimed to observe the associations of tagging SNPs in Tanis gene with fasting plasma TG levels in Chinese Han and Uygur population in Xinjiang, the western China.

Results and discussion
This study consists of two ethnic groups (Han: n=1059; Uygur: n=438). The clinical and metabolic characteristics of the study population are shown separately for Han and Uygur in Table 1.

All genotyped SNPs were in Hardy-Weinberg equilibrium (all P>0.05, data not shown). Table 2 shows detailed information for each SNP as well as the allele frequencies.

Table 1 Demographic and risk profile of the study population

| Risk factors        | No. (%) or Mean±SD | P values |
|---------------------|---------------------|----------|
| Age (years)         | Han (n=1059)        | Uygur (n=438) |
|                      | 60.38 ± 11.81       | 63.16 ± 10.70 | <0.001 |
| Female (%)          | 481 (45.4)          | 174 (39.7)    | 0.043  |
| Never drink (%)     | 837 (79.0)          | 393 (89.7)    | <0.001 |
| Former drinker (%)  | 201(19.0)           | 24 (5.5)      |        |
| Current drinker (%) | 21 (2.0)            | 21 (4.8)      |        |
| Never smoking (%)   | 689 (65.1)          | 331 (75.6)    | <0.001 |
| Former smoking (%)  | 298 (28.1)          | 72 (16.4)     |        |
| Current smoking (%) | 72 (6.8)            | 35 (8.0)      |        |
| BMI (Kg/m²)         | 24.52 ± 3.40        | 24.99 ± 3.99  | 0.020  |
| SBP (mmHg)          | 122.21 ± 13.11      | 120.64 ± 10.07 | 0.025  |
| DBP (mmHg)          | 76.75 ± 10.66       | 73.46 ± 7.40  | <0.001 |
| GLU (mmol/L)        | 4.57 ± 0.86         | 4.30 ± 0.45   | <0.001 |
| TG (mmol/L)         | 0.96 ± 0.34         | 0.93 ± 0.35   | 0.080  |
| TC (mmol/L)         | 4.26 ± 0.98         | 4.12 ± 0.94   | 0.015  |
| HDL (mmol/L)        | 1.28 ± 0.44         | 1.27 ± 0.47   | 0.172  |
| LDL-C (mmol/L)      | 2.65 ± 0.81         | 2.54 ± 0.80   | 0.016  |

Note: HDL high-density lipoprotein, LDL low-density lipoprotein, SBP Systolic blood pressure, DBP Diastolic blood pressure, TG Triglycerides, TC Cholesterol, BMI Body mass index, GLU Glucose.

Table 2 Distributions of SNPs of Tanis gene in Han and Uygur population

| SNPs     | Genotypes | Ethnic | P value |
|----------|-----------|--------|---------|
| rs12910524 | TT        | Han    | 158 (14.9) | 0.046 |
|          | CC        | Han    | 415 (39.2) |       |
|          | TC        | Han    | 486 (45.9) |       |

Both in Chinese Han and Uygur populations, we found that the rs12910524 was significantly associated with plasma TG levels in a dominant model, additive model, or recessive model before (All P <0.001) and after multivariate adjustment (All P <0.001; Table 3). However, these associations were not found in rs1384565, rs2101171, and rs4965814 before and after adjustment of confounders. Furthermore, using the general linear model analysis, we found that the GLU level was significantly associated with TG level both in Han (P=0.001) and Uygur populations (P=2.99×10⁻⁶). And, we also found significant interactions between rs12910524 and GLU on plasma TG both in Han (P=0.001; Table 4) and Uygur populations (P=2.60×10⁻⁴; Table 5). However, we did not find any interaction between rs1384565, rs2101171, and rs4965814 and GLU level (Table 4, Table 5).

In Chinese Uygur population, we found that the rs12910524 was significantly associated with plasma TC levels in a dominant model, additive model, or recessive model before (All P <0.01) and after multivariate adjustment (All P <0.01; Table 6). And we also found that the rs12910524 was significantly associated with plasma LDL-C level in a recessive model and an additive model before (All P <0.01) and after multivariate adjustment (All P <0.01; Table 7). In addition, we found the rs1384565 was significantly associated with plasma HDL-C level in a dominant model and in an additive model after multivariate adjustment (both P <0.01; Table 8). However, we did not find any association of Tanis genetic polymorphisms with plasma TC, HDL-C, and LDL-C levels in Chinese Han population.

In this study, we observed that variation in the Tanis gene was associated with plasma TG levels in Chinese subjects. Individuals with the C allele of rs12910524 had significantly higher plasma TG levels when compared with TT genotype carriers. To our knowledge, this is the
first study to investigate the common allelic variant in Tanis gene and its association with plasma TG levels. The human Tanis gene is located at 15q26.3. Although this region has not been previously identified in genome-wide linkage scans for diabetes-related phenotypes in human populations, previous studies [25] indicated that the Tanis gene expression was positively correlated to BMI, plasma levels of TG and HDL cholesterol, insulin, and blood glucose levels. Also, several studies suggested that the variations in Tanis gene were associated with inflammation [23], coronary heart disease (CHD) and ischemic stroke [24], and metabolic disease [25]. The plasma triglyceride level is known to be influenced by a large number of factors, including age, sex, hypertension, diabetes, smoking and alcohol intake. Our findings show that rs1291054 is an independent determinant of triglyceride level, and does not influence the level by modulating some confounding factors such as age, sex, smoking, BMI, and alcohol intake. Walder et al. [19] described the biological characteristics of Tanis first. In their study, they found that Tanis gene expression was increased 2.2-fold after a 24-h fast in *P. obesus*, a polygenic animal model of type 2 diabetes and metabolic syndrome. Also, they found that there was a positive correlation between Tanis expression and circulating TG concentrations (Pearson r = 0.593, P = 0.007); as well as blood glucose (Spearman r = 0.378, P = 0.010) and insulin concentrations (Spearman r = 0.416, P = 0.004). However, subsequently multiple linear regression analysis indicated that only the change in blood glucose concentration was

| Source | Type III sum of squares | df | Mean square | F | Sig. |
|---|---|---|---|---|---|
| Corrected model | 15.139* | 13 | 1.165 | 8.322 | 3.50×10-16 |
| Age | 0.051 | 1 | 0.051 | 0.365 | 0.546 |
| Sex | 0.030 | 1 | 0.030 | 0.216 | 0.642 |
| Smoking | 0.012 | 1 | 0.012 | 0.085 | 0.771 |
| Drinking | 0.117 | 1 | 0.117 | 0.838 | 0.360 |
| BMI | 0.028 | 1 | 0.028 | 0.202 | 0.653 |
| rs12910524 | 2.036 | 2 | 1.018 | 7.273 | 0.001 |
| GLU * rs12910524 | 0.933 | 3 | 0.311 | 2.222 | 0.012 |
| GLU * rs4965814 | 0.283 | 1 | 0.283 | 2.021 | 0.155 |
| GLU * rs2101171 | 0.232 | 1 | 0.232 | 1.658 | 0.198 |
| GLU * rs1384565 | 0.312 | 1 | 0.312 | 2.227 | 0.136 |
| Error | 146.240 | 1045 | 0.140 | |
| Total | 173.988 | 1059 | | |
| Corrected total | 161.380 | 1058 | | |

*R Squared = 0.094 (Adjusted R Squared = 0.083).
independently associated with Tanis gene expression. This result suggests that the association of Tanis gene expression with TG level can be modified by blood glucose level. Therefore, in this study, we excluded the diabetic patients when we selected participants at the beginning of the study, and we found that in nondiabetic subjects, the rs12910524 was independently associated with plasma TG level, and this relationship was not modified by the fasting blood glucose level. And this association was observed not only in Chinese Han but also in Chinese Uygur population.

We also analyzed the associations of Tanis genetic polymorphisms with plasma TC, HDL-C, and LDL-C levels. In Chinese Uygur population, we found that the rs12910524 was significantly associated with plasma TC levels and plasma LDL-C levels. And, we also found that the rs1384565 was significantly associated with plasma HDL-C levels. However, we did not find any association of Tanis genetic polymorphisms with plasma TC, HDL-C, and LDL-C levels in Chinese Han population. This discrepancy may be explained by the different distributions of Tanis genetic polymorphisms and some confounders between Chinese Han and Uygur population.

In addition, some published data indicated that inflammatory genes may regulate fasting TG levels [26]. And previous studies also indicated that Tanis gene was associated with inflammatory cytokines [23]. In the present study, we found Tanis genetic polymorphism was associated with TG level. However we have no evidences to demonstrate whether this association was related to inflammation because of the absence of some inflammatory cytokines parameters. Otherwise, because of the absence of some confounders such as plasma HOMA-IR or HbA1c levels, eating habits, working pressure and the social disparities in our database, we did not include these variables in the multivariate analysis. This fact is a limitation of our study.

Table 6 Association of Tanis SNPs with TC in Han and Uygur population

|          | Mean TC level | Model 1‡ | Model 2§ |
|----------|---------------|----------|----------|
|          | Homozygous for rare allele | Heterozygous | Homozygous for wild allele |
|          | P Rec* | P Domt | P Add† | P Rec* | P Domt | P Add† |
| Han      |        |        |        |        |        |        |
| rs12910524 C/T | 4.11 ± 1.13 | 4.24 ± 0.95 | 4.34 ± 0.92 | 0.047 | 0.034 | 0.042 | 0.062 | 0.107 | 0.10 |
| rs1384565 T/C | 4.26 ± 1.01 | 4.30 ± 0.99 | 4.22 ± 0.99 | 0.265 | 0.098 | 0.510 | 0.493 | 0.761 | 0.692 |
| rs2101171 T/C | 4.09 ± 1.01 | 4.24 ± 0.95 | 4.26 ± 0.97 | 0.479 | 0.330 | 0.553 | 0.529 | 0.142 | 0.328 |
| rs4965814 T/C | 4.17 ± 1.03 | 4.29 ± 0.98 | 4.26 ± 0.92 | 0.955 | 0.184 | 0.362 | 0.757 | 0.274 | 0.549 |
| Uygur    |        |        |        |        |        |        |
| rs12910524 C/T | 3.62 ± 0.99 | 4.13 ± 0.93 | 4.28 ± 0.89 | <0.001 | 0.003 | <0.001 | <0.001 | 0.005 | <0.001 |
| rs1384565 T/C | 3.59 ± 1.19 | 4.15 ± 0.93 | 4.13 ± 0.94 | 0.731 | 0.058 | 0.163 | 0.655 | 0.079 | 0.213 |
| rs2101171 T/C | 4.13 ± 0.94 | 4.06 ± 0.94 | 4.38 ± 1.05 | 0.391 | 0.622 | 0.530 | 0.498 | 0.535 | 0.570 |
| rs4965814 T/C | 4.08 ± 1.03 | 4.09 ± 0.97 | 4.18 ± 0.88 | 0.310 | 0.689 | 0.597 | 0.361 | 0.526 | 0.625 |

‡Analysis of covariance adjusted for sex, age, smoking, alcohol drinking, and GLU; †Unadjusted model; *recessive model; ‡dominant model; ††additive model.

Table 7 Association of Tanis SNPs with LDL-C in Han and Uygur population

|          | Mean LDL-C level | Model 1‡ | Model 2§ |
|----------|------------------|----------|----------|
|          | Homozygous for rare allele | Heterozygous | Homozygous for wild allele |
|          | P Rec* | P Domt | P Add† | P Rec* | P Domt | P Add† |
| Han      |        |        |        |        |        |        |
| rs12910524 C/T | 2.55 ± 0.93 | 2.61 ± 0.79 | 2.72 ± 0.77 | 0.091 | 0.014 | 0.032 | 0.126 | 0.034 | 0.071 |
| rs1384565 T/C | 2.71 ± 0.90 | 2.70 ± 0.82 | 2.60 ± 0.78 | 0.043 | 0.502 | 0.128 | 0.119 | 0.731 | 0.295 |
| rs2101171 T/C | 2.38 ± 0.80 | 2.60 ± 0.74 | 2.68 ± 0.83 | 0.051 | 0.069 | 0.057 | 0.052 | 0.036 | 0.037 |
| rs4965814 T/C | 2.55 ± 0.84 | 2.68 ± 0.82 | 2.65 ± 0.77 | 0.970 | 0.070 | 0.163 | 0.869 | 0.151 | 0.339 |
| Uygur    |        |        |        |        |        |        |
| rs12910524 C/T | 2.25 ± 0.80 | 2.52 ± 0.81 | 2.64 ± 0.78 | 0.003 | 0.022 | 0.004 | 0.005 | 0.025 | 0.007 |
| rs1384565 T/C | 2.02 ± 0.84 | 2.52 ± 0.78 | 2.56 ± 0.81 | 0.312 | 0.032 | 0.091 | 0.323 | 0.036 | 0.102 |
| rs2101171 T/C | 2.54 ± 0.79 | 2.53 ± 0.86 | 2.57 ± 0.80 | 0.905 | 0.951 | 0.988 | 0.888 | 0.945 | 0.990 |
| rs4965814 T/C | 2.40 ± 0.47 | 2.55 ± 0.82 | 2.58 ± 0.80 | 0.395 | 0.117 | 0.280 | 0.447 | 0.106 | 0.267 |

§Analysis of covariance adjusted for sex, age, smoking, alcohol drinking, and GLU; †Unadjusted model; *recessive model; ‡dominant model; ††additive model.
Conclusions
In conclusion, our results indicate that the Tanis gene rs12910524 polymorphism is an important and clinically relevant determinant of plasma TG levels in the Chinese subjects without diabetes.

Subjects and methods

Subjects
This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University and was conducted according to the standards of the Declaration of Helsinki. Written informed consent was obtained from the participants. All the participants were selected from the Cardiovascular Risk Survey (CRS) study which was described in the previous studies [27,28]. From these subjects participating in CRS (n=14618), we selected 1821 participants who were free from diabetes, hypertension, any history of CAD, or any history of taking lipid-lowering drugs. We defined diabetes by using the American Diabetes Association (ADA) 2009 criteria as described previously [29] (fasting plasma glucose ≥7.0 mmol/L [≥126 mg/dL]) or self-reported current diabetes treatments in the survey. Among these 1821 participants, only 1740 (Han: n= 1251; Uygur: n= 489) participants consented to providing blood samples for DNA analysis. We excluded 243 hypertriglyceridemia (fasting plasma TG ≥1.7 mmol/L) patients during the analysis. The analysis presented in this study was based on 1497 subjects (Han: n= 1059; Uygur: n= 438) who had passed the eligibility criteria and had complete data on Tanis genotype.

Biological and lifestyle measurements
Height, body weight, and blood pressure were measured as described previously [27,28]. Smoking and drinking status was self-reported by study questionnaire as described previously [27,28]. We measured the fasting plasma concentration of total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and glucose using an equipment for chemical analysis (Dimension AR/AVL Clinical Chemistry System, Newark, NJ) employed by the Clinical Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University as described previously [27-31].

Tanis single-nucleotide polymorphism genotyping
There are 190 SNPs for the human Tanis gene listed in the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP).

We also screened the data for the Tag SNPs on the International HapMap Project website (http://www.hapmap.org/). Using the Haploview 4.2 software and the HapMap phase II database, we obtained four tagging SNPs (rs12910524, rs1384565, rs2101171, and rs4965814) for Chinese Han using minor allele frequency (MAF) ≥0.05 and linkage disequilibrium patterns with r2 ≥0.8 as a cutoff. Genomic DNA was extracted from the peripheral blood leukocytes using a DNA extraction Kit (Beijing Biotekte Co. Ltd, China). Genotyping was confirmed using TaqMan® assays from Applied Biosystems following the manufacturer’s suggestions and analyzed in an ABI 7900HT Fast Real-Time PCR System. To ensure the results to be verified, of the genotyped samples, 10% were duplicated and there was at least one positive and one negative control per 96-well DNA plate in our assays. The accuracy of the genotyping was determined by the genotype concordance between duplicate samples. We obtained a 100% concordance between the genotyped duplicate samples.

Statistical analysis
All analyses were carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The Hardy-Weinberg equilibrium was assessed using chi-square analysis. The

Table 8 Association of Tanis SNPs with HDL-C in Han and Uygur population

|                | Wild/Rare allele | Mean HDL-C level |         |         |         |         |         |         |         |         |         |         |         |
|----------------|------------------|------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                | Homozygous for    | Heterozygous     | Homozygous for | P Rec* | P Dom† | P Add‡ | P Rec* | P Dom† | P Add‡ |         |         |         |         |
|                | rare allele       |                  | wild allele   |        |        |        |        |        |        |        |        |        |        |
| Han            | rs12910524       | C/T              | 1.28 ± 0.41  | 1.32 ± 0.44 | 1.30 ± 0.46 | 0.428   | 0.607   | 0.518   | 0.505   | 0.388   | 0.414   |         |         |
|                | rs1384565        | T/C              | 1.32 ± 0.54  | 1.31 ± 0.45 | 1.30 ± 0.42 | 0.499   | 0.772   | 0.792   | 0.516   | 0.682   | 0.787   |         |         |
|                | rs2101171        | T/C              | 1.27 ± 0.52  | 1.31 ± 0.44 | 1.31 ± 0.44 | 0.996   | 0.673   | 0.910   | 0.974   | 0.470   | 0.752   |         |         |
|                | rs4965814        | T/C              | 1.27 ± 0.47  | 1.31 ± 0.44 | 1.32 ± 0.43 | 0.442   | 0.215   | 0.430   | 0.289   | 0.186   | 0.335   |         |         |
| Uygur          | rs12910524       | C/T              | 1.19 ± 0.42  | 1.24 ± 0.40 | 1.33 ± 0.54 | 0.127   | 0.025   | 0.059   | 0.285   | 0.065   | 0.062   |         |         |
|                | rs1384565        | T/C              | 1.64 ± 1.72  | 1.31 ± 0.34 | 1.25 ± 0.40 | 0.073   | 0.0007  | 0.014   | 0.103   | 0.002   | 0.007   |         |         |
|                | rs2101171        | T/C              | 1.28 ± 0.50  | 1.22 ± 0.35 | 1.51 ± 0.51 | 0.096   | 0.498   | 0.131   | 0.341   | 0.347   | 0.126   |         |         |
|                | rs4965814        | T/C              | 1.39 ± 0.77  | 1.25 ± 0.38 | 1.25 ± 0.39 | 0.413   | 0.025   | 0.082   | 0.424   | 0.047   | 0.193   |         |         |

‡Analysis of covariance adjusted for sex, age, smoking, alcohol drinking, and GLU; †Unadjusted model; *recessive model; †dominant model; ‡additive model.
characteristics of the study population were expressed as the mean ± standard deviation or as a ratio. Fasting triglycerides were log-transformed using natural logarithms for analysis. General linear model analysis was undertaken to test for associations between SNP genotypes and TG levels after adjusting for confounding variables. Single-SNP effects with continuous variables were analyzed using linear regression using three models. These were the additive (common allele homozygotes coded as 1, heterozygotes as 2, and recessive allele homozygotes as 3); dominant (common allele homozygotes coded as 1 and heterozygotes and recessive allele homozygotes as 2); and recessive (common allele homozygotes and heterozygotes coded as 1 and recessive allele homozygotes as 2) models as described previously [16]. Normality was assessed by plotting the residuals. To assess the association of each SNP with TG level, we used a Bonferroni correction to control for the number of variants tested; this was 4, so the probability value, 0.0125, was considered to be significant.

Abbreviations
SNP: Single nucleotide polymorphisms; CAD: Coronary artery disease; SAA: Serum amyloid A; TG: Triglycerides; TC: Total cholesterol; HDL-C: High-density lipoprotein; LDL-C: Low-density lipoprotein.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
YG and XX carried out the molecular genetic studies and drafted the manuscript. YNY, ZYF and XML carried out the genotyping. XM, YC, and BDC conceived of the study and participated in its design and manuscript. YTY, YH, FL and YYZ participated in the design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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