**BMC
Medical Genetics**

RESEARCH ARTICLE   **Open Access**

Lack of association between genetic polymorphisms within *DUSP12 - ATF6* locus and glucose metabolism related traits in a Chinese population

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Abstract

Background: Genome-wide linkage studies in multiple ethnic populations found chromosome 1q21-q25 was the strongest and most replicable linkage signal in the human chromosome. Studies in Pima Indian, Caucasians and African Americans identified several SNPs in *DUSP12* and *ATF6*, located in chromosome 1q21-q23, were associated with type 2 diabetes.

Methods: We selected 19 single nucleotide polymorphisms (SNPs) that could tag 98% of the SNPs with minor allele frequencies over 0.1 within *DUSP12-ATF6* region. These SNPs were genotyped in a total of 3,700 Chinese Han subjects comprising 1,892 type 2 diabetes patients and 1,808 controls with normal glucose regulation.

Results: None of the SNPs and haplotypes showed significant association to type 2 diabetes in our samples. No association between the SNPs and quantitative traits was observed either.

Conclusions: Our data suggests common SNPs within *DUSP12-ATF6* locus may not play a major role in glucose metabolism in the Chinese.

Background

Type 2 diabetes is a complex disease caused by both genetic and environmental factors. Although recent genome-wide association studies have identified several novel, possibly causative genes, the contribution of them to disease risk is still very limited [1]. Thus the genetic architecture of type 2 diabetes remained largely unknown. Previous genome-wide linkage studies in multiple ethnic populations, including Caucasians, Chinese and Pima Indian, showed that chromosome 1q21-q25 was the strongest and most replicable linkage signal in the human chromosome [2-9]. Although genome-wide association studies show no strong association signal in this region, whether variants harbored in this region conferred modest effect to the disease are worthy to be analyzed.

Dual specificity phosphatase 12 (*DUSP12*) and activating transcription factor 6 (*ATF6*) were two neighbored genes locating on the chromosome 1q21-q23. DUSP12 is a

glucokinase - associated protein identified from rat hepatic cDNA library through yeast two-hybrid, using glucokinase as bait. It may participate in glycolysis in the liver and pancreatic beta-cell through dephosphorylation of glucokinase in the cytoplasm [10]. *ATF6* is a key sensor of endoplasmic reticulum stress. It activates unfolded protein response through regulating a group of genes encoding molecular chaperones and folding enzymes [11]. Previous studies identified several single nucleotide polymorphisms (SNPs) in this region associated with type 2 diabetes in different populations. Among them, rs2070150 (P145A) was firstly identified to be associated with type 2 diabetes in Pima Indian, while rs4579731, rs3820449 and rs10918215 were reported later in studies focusing on Caucasians and African Americans [12-15]. However, International Type 2 Diabetes 1q Consortium failed to detect any association signal on *DUSP12* and *ATF6* in a fine mapping study in multiethnic samples [16]. Even though, only 285 East Asian origin samples were included in the previous studies and no one analyzed the association between SNPs from this region and type 2 diabetes in large Asian samples. Therefore, we performed the present study, aiming to test

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if variants from *DUSP12* and *ATF6* played a role in the genetic susceptibility of type 2 diabetes in the Chinese.

Methods

Participants

In this case-control study, we recruited 3,700 unrelated Chinese Han subjects, including 1,892 case and 1,808 controls. All the subjects were eastern Chinese Han ancestry, residing in Shanghai and nearby region. In the present study, all case subjects were type 2 diabetes patients selected from Shanghai Diabetes Institute inpatient database. Control subjects were community-based populations enrolled from the Shanghai Diabetes Studies [17]. The inclusion and exclusion criteria for the cases and controls were described previously [17]. Briefly, all cases were type 2 diabetes patients defined according to 1999 WHO criteria (fasting plasma glucose ≥7.0 mmol/l and/or 2-h plasma glucose ≥11.1 mmol/l) and were treated with oral hypoglycemic agents and/or insulin. The control subjects were normal glucose tolerance defined based on fasting plasma glucose <6.1 mmol/l and 2-h plasma glucose <7.8 mmol/l. This study was approved by the institutional review board of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent was obtained from each participant.

Clinical measurement

All subjects underwent detailed clinical investigations, as described previously [17]. Briefly, anthropometric parameters such as height, weight, waist and hip circumference (for the control subjects only) were measured. For the control subjects, blood samples were obtained at 0 and 120 min during the oral glucose tolerance tests (OGTTs) to measure plasma glucose and serum insulin levels. Lipid profiles such as total cholesterol and triglyceride were also obtained. Insulin resistance and pancreatic β-cell function were assessed by homeostasis model assessment (HOMA) [18]. HOMA-IR = fasting insulin × fasting plasma glucose ÷ 22.5, HOMA-B = 20 × fasting insulin ÷ (fasting plasma glucose ÷ 3.5).

SNPs selection, genotyping and quality control

We selected 19 SNPs that spanning 197 kb of *DUPS12* and *ATF6* region, from 10 kb 5' upstream the *DUSP12* to 2 kb 3' downstream the *ATF6*. These SNPs could tag 98% of the SNPs with MAF over 0.1 derived from HapMap Phase III Chinese Han database under the threshold of r^2 ≥0.7. Among them, 7 SNPs located in the coding region. The SNPs previously reported were either directly genotyped or in linkage disequilibrium (LD) with genotyped SNPs. All the SNPs were genotyped using Sequenom's MassARRAY iPLEX system (MassARRAY Compact Analyzer, Sequenom, San Diego, CA, USA). The key quality control requirements were: 1) sample call rates ≥75%; 2) SNP call rate ≥85%; 3) less than two discrepant genotypes of 100 duplicate samples; and 4) Hardy-Weinberg equilibrium test ≥0.05 in controls and cases respectively. After the quality control procedures of the genotypes, 71 individuals were excluded. And one SNP (rs3767635) failed Hardy-Weinberg equilibrium test. The average call rate for the remaining 18 SNPs was 97.5%, and the average concordance rate based on 100 duplicate comparisons for each SNP was 99.4%. Detailed information of the call rates and concordance rates for the SNPs was shown in the Additional file 1 Table S1.

Statistical analyses

Observed genotypes were tested for fit to the expectation of Hardy-Weinberg equilibrium using χ^2 test. Pairwise LD was estimated from the combined data of cases and controls calulating |D'| and r^2 using Haploview (version 4.1) http://www.broadinstitute.org/haploview/haploview [19]. Haplotype block structure was determined using confidence interval algorithm [20] and haplotype frequencies were estimated by Expectation-Maximization algorithm [21] using Haploview (v 4.1). Allele, genotype and haplotype frequencies for cases and controls were compared using χ^2 test or Fisher's exact test. Odds ratios (ORs) with 95% confidence intervals (CIs) were presented. The genotype - disease association analyses were performed under the additive model adjusting age, gender and BMI as confounding factors by logistic regression. Quantitative traits with skewed distribution were natural logarithmically transformed to approximate univariate normality. Quantitative traits were analyzed under an additive genetic model by linear regression adjusted for age, sex, and BMI. All statistical analyses were performed by SAS (version 8.0; SAS Institute Inc., Cary, NC, USA) unless specified otherwise. A two-tailed *P* value <0.05 was considered significant. The allele frequencies in HapMap populations and statistic power of the SNPs were shown in the Additional file 2 Table S2.

Results

A total of 18 SNPs were successfully genotyped in 3,629 individuals in the present study. The LD pattern of these SNPs was shown in Figure 1. Three haplotype blocks were constructed in this region.

The single SNP association analysis showed that no SNP was significantly associated with type 2 diabetes in our samples. The minimum *P* value was 0.0954 for rs10799941. Logistic regression analysis adjusting age, gender and BMI as confounding factors also suggested no association between SNPs and type 2 diabetes (Table 1). For the haplotype analysis, we compared the haplotype distributions between cases and controls and observed that no haplotype was nominally associated with type 2 diabetes (Table 2).
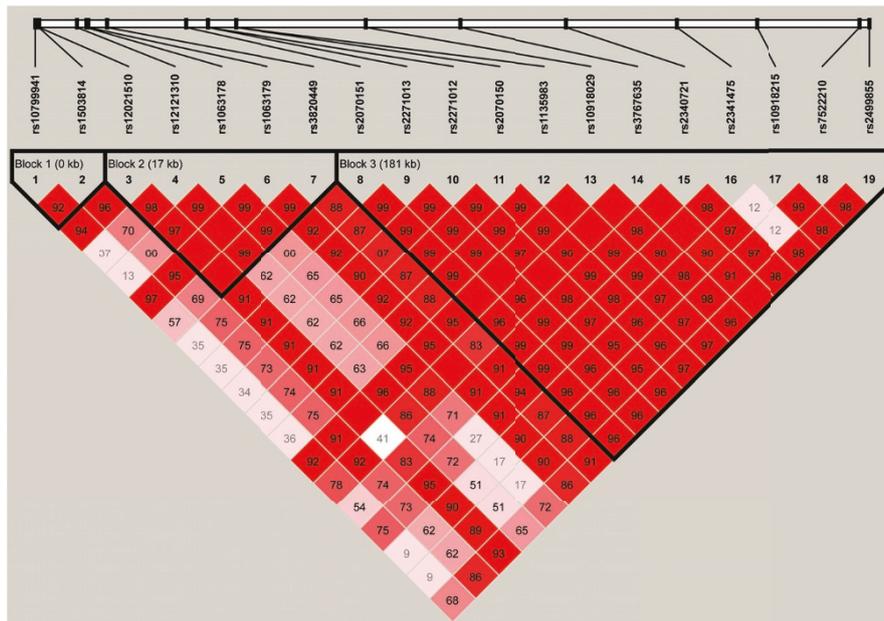
Figure 1 Linkage disequilibrium plots for SNPs genotyped in *DUSP12 - ATF6* locus in the Chinese samples. Shades of pink indicate the strength of pairwise LD based on |D′|. Number shown are |D′| of each SNP pair.

We then analyzed the association between SNPs and quantitative traits related to glucose metabolism in the individuals with normal glucose regulation. No SNP was associated with plasma glucose and serum insulin levels at fasting status as well as 2-h after glucose stimulation. No significant association was detected between insulin sensitivity and beta cell function either (Table 3).

Discussion

Genome-wide linkage studies in various populations suggested the existence of multiple susceptibility gene(s) for type 2 diabetes at chromosome 1q21-q24 [2-9]. Several specific genes in this region, such as *LMNA*, *NOS1AP* and *ATF6*, were identified that they might confer risk for diabetes in some populations [12-16,22-24].

Table 1 Allele frequencies and association to type 2 diabetes for SNPs in the *DUSP12-ATF6* locus

Gene	SNP	Chromosome position	Major/minor allele	Risk allele	Risk allele frequency		OR (95%CI)	P_{allele}	$P_{genotype}$
					Cases	Controls			
DUSP12	rs10799941	159974818	T,G	T	0.540	0.520	1.0821(0.9863-1.1873)	0.0954	0.1122
DUSP12	rs1503814	159975743	C,T	T	0.329	0.316	1.0613(0.9616-1.1714)	0.2373	0.3788
DUSP12	rs12021510	159975835	A,G	A	0.930	0.929	1.0141(0.8466-1.2147)	0.8794	0.9472
DUSP12	rs12121310	159985839	A,C	C	0.379	0.367	1.0546(0.9572-1.1620)	0.2823	0.5793
DUSP12	rs1063178	159988331	C,T	T	0.460	0.458	1.0074(0.9177-1.1060)	0.8766	0.7165
DUSP12	rs1063179	159988828	C,T	C	0.772	0.762	1.0594(0.9498-1.1817)	0.3002	0.3300
DUSP12	rs3820449	159993796	C,T	C	0.694	0.694	1.0002(0.9049-1.1056)	0.9964	0.6854
ATF6	rs2070151	160014680	C,T	T	0.311	0.300	1.0512(0.9511-1.1619)	0.3282	0.2568
ATF6	rs2271013	160020426	A,G	G	0.310	0.300	1.0506(0.9505-1.1612)	0.3338	0.2515
ATF6	rs2271012	160020465	C,T	T	0.317	0.302	1.0706(0.9666-1.1858)	0.1908	0.1373
ATF6	rs2070150	160027900	G,C	C	0.312	0.301	1.0568(0.9559-1.1685)	0.2805	0.2015
ATF6	rs1135983	160027936	C,T	T	0.309	0.297	1.0563(0.9553-1.1680)	0.2856	0.2305
ATF6	rs10918029	160062520	G,A	G	0.780	0.774	1.0360(0.9272-1.1575)	0.5326	0.6230
ATF6	rs2340721	160116009	A,C	C	0.349	0.344	1.0197(0.9247-1.1244)	0.6959	0.9399
ATF6	rs2341475	160145232	G,A	G	0.658	0.646	1.0531(0.9497-1.1677)	0.3268	0.4704
ATF6	rs10918215	160166355	A,G	G	0.432	0.427	1.0223(0.9304-1.1234)	0.6460	0.4317
ATF6	rs7522210	160193803	C,G	G	0.433	0.427	1.0258(0.9341-1.1264)	0.5940	0.3425
ATF6	rs2499855	160196385	A,G	A	0.897	0.890	1.0753(0.9203-1.2563)	0.3606	0.5117

Table 2 Association analyses of haplotypes in DUSP12-ATF6 locus with type 2 diabetes

Haplotype	Haplotype frequencies		P value
	Cases	Controls	
Block 1 (rs10799941-rs1503814)			
GC	0.449	0.467	0.1199
TT	0.318	0.304	0.1919
TC	0.222	0.217	0.5799
GT	0.011	0.013	0.5919
Block 2 (rs12021510-rs12121310-rs1063178-rs1063179-rs3820449)			
ACTCT	0.307	0.306	0.8928
AACCC	0.242	0.236	0.5579
AACTC	0.228	0.237	0.3592
AATCC	0.080	0.089	0.1618
GACCC	0.070	0.069	0.8911
ACTCC	0.074	0.064	0.0897
Block 3 (rs2070151-rs10918029-rs7522210-rs2499855)			
CGCA	0.342	0.341	0.9407
TGGA	0.304	0.296	0.4348
CACA	0.218	0.226	0.3917
CGGG	0.100	0.107	0.3166
CGGA	0.021	0.017	0.3030

Among these genes, *ATF6* is a strong candidate by its biological function in endoplasmic reticulum stress and unfolded protein response, which linked insulin demand with beta cell failure and diabetes. ATF6 is also the binding target of WFS1, a known type 2 diabetes susceptible gene, and mediates its effect on endoplasmic reticulum stress [25]. However, although we performed the association study by analyzing 18 SNPs in 3700 Chinese Han, we failed to find any evidence of association between SNPs from this locus and traits related to glucose metabolism in our samples. One possible explanation might be that the statistical power of our samples was not enough to detect the effects of this locus in the Chinese population. Although we had over 80% power to detect the association at the 0.05 level based on the previously reported ORs in non-Asian populations (1.2 ~ 1.3) and allele frequencies of reported SNPs in our Chinese samples, we could not exclude the possibility the reported effect size was overestimated due to the "winner's curse" effect or novel associated SNPs with lower minor allele frequencies in the Chinese existed, in this case our samples may not have sufficient power. Secondly, the relatively loose criteria for tagging SNP selection, which is the limitation of the current study, missed information for a group of SNPs in this region. As we used r^2 over 0.7 and minor allele frequency over 0.1 as SNPs selection criterion, we failed to capture 15 (6.8%) SNPs if the stringent criterion r^2 over 0.8 and minor allele frequency over 0.05 was adopted. Thirdly, the LD pattern and allele frequencies differed between Chinese Hans and previously studied populations, which suggested population differences in the genetic architecture between Chinese and other ethnic populations, may also partly explain the lack of association between this locus and previously reported phenotypes. Finally we cannot exclude the possibility that rare variants within

Table 3 Association between SNPs from *DUSP12-ATF6* and clinical features related to glucose metabolism in the normal glucose regulation subjects

SNP	Fasting glucose			2 h glucose			Fasting insulin			HOMA-IR			HOMA-B		
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
rs10799941	0.0065	0.0164	0.6933	0.0325	0.0387	0.4024	-0.0087	0.0226	0.7019	-0.0076	0.0237	0.7492	-0.0164	0.0249	0.5116
rs1503814	0.0098	0.0179	0.5833	0.0247	0.0425	0.5613	0.0023	0.0251	0.9273	0.0065	0.0262	0.8036	-0.0135	0.0277	0.6264
rs12021510	0.0073	0.0322	0.8203	-0.0795	0.0760	0.2953	0.0039	0.0452	0.9319	0.0054	0.0473	0.9086	-0.0021	0.0499	0.9670
rs12121310	0.0288	0.0173	0.0963	0.0740	0.0411	0.0719	-0.0066	0.0241	0.7858	0.0010	0.0253	0.9678	-0.0400	0.0267	0.1346
rs1063178	0.0298	0.0165	0.0722	0.0356	0.0392	0.3639	0.0083	0.0230	0.7192	0.0162	0.0240	0.5008	-0.0259	0.0254	0.3068
rs1063179	-0.0178	0.0192	0.3541	0.0082	0.0454	0.8561	-0.0241	0.0262	0.3590	-0.0258	0.0274	0.3483	-0.0090	0.0288	0.7552
rs3820449	0.0216	0.0178	0.2256	0.0739	0.0421	0.0791	-0.0179	0.0247	0.4687	-0.0113	0.0259	0.6627	-0.0489	0.0273	0.0737
rs2070151	-0.0187	0.0184	0.3094	-0.0112	0.0435	0.7970	0.0023	0.0254	0.9295	-0.0061	0.0266	0.8182	0.0328	0.0280	0.2426
rs2271013	-0.0203	0.0184	0.2704	-0.0126	0.0435	0.7728	0.0014	0.0252	0.9559	-0.0073	0.0264	0.7822	0.0330	0.0278	0.2367
rs2271012	-0.0196	0.0186	0.2934	-0.0193	0.0440	0.6615	0.0086	0.0257	0.7376	0.0004	0.0269	0.9883	0.0376	0.0285	0.1866
rs2070150	-0.0177	0.0185	0.3397	-0.0154	0.0438	0.7249	0.0062	0.0257	0.8106	-0.0020	0.0269	0.9405	0.0349	0.0283	0.2178
rs1135983	-0.0168	0.0185	0.3633	-0.0192	0.0438	0.6609	0.0128	0.0256	0.6180	0.0046	0.0268	0.8642	0.0427	0.0283	0.1314
rs10918029	0.0075	0.0197	0.7027	0.0282	0.0467	0.5451	-0.0102	0.0271	0.7066	-0.0071	0.0284	0.8029	-0.0177	0.0300	0.5561
rs2340721	-0.0023	0.0174	0.8958	0.0488	0.0410	0.2342	-0.0074	0.0239	0.7581	-0.0064	0.0250	0.7988	-0.0125	0.0264	0.6346
rs2341475	0.0202	0.0187	0.2810	-0.0207	0.0445	0.6419	0.0021	0.0257	0.9350	0.0093	0.0269	0.7299	-0.0226	0.0289	0.4332
rs10918215	0.0022	0.0167	0.8941	-0.0441	0.0396	0.2647	0.0120	0.0232	0.6054	0.0093	0.0243	0.7006	0.0193	0.0256	0.4501
rs7522210	0.0001	0.0166	0.9945	-0.0425	0.0394	0.2809	0.0095	0.0230	0.6810	0.0061	0.0241	0.8001	0.0213	0.0253	0.3991
rs2499855	0.0153	0.0266	0.5654	-0.0842	0.0630	0.1814	0.0172	0.0367	0.6391	0.0199	0.0384	0.6045	0.0023	0.0407	0.9546

this region participated in the pathogenesis of diabetes as we only focused on the common ones.

Conclusion

Our data suggests common variants within *DUSP12* and *ATF6* genes may not play a major role in glucose metabolism in the Chinese. However, due to the limitation of the current study, the effects of SNPs from this locus on type 2 diabetes need to be tested in further studies with larger East Asian origin samples and higher marker density.

Additional material

Additional file 1: Call rates and concordance rates of SNPs genotyped. This file contains detailed information of quality control analysis of the SNPs, including call rates and concordance rates.

Additional file 2: Allele frequencies and statistic power of the SNPs. This file contains the allele frequencies of all SNPs in the HapMap populations and our samples. The statistic power of the SNPs in our samples was also shown in this file.

List of abbreviations

ATF6: activating transcription factor 6; CI: confidence interval; DUSP12: dual specificity phosphatase 12; HOMA: homeostasis model assessment; LD: linkage disequilibrium; OGTT: oral glucose tolerance test; OR: odds ratio; SNP: single nucleotide polymorphism;

Authors' contributions

CH designed the study, participated in genotyping, performed statistical analysis and drafted the manuscript. RZ prepared the DNA samples and participated in genotyping. CW participated in genotyping. XM participated in sample collection and clinical studies. JW participated in the clinical study and revised the manuscript. YB participated in clinical study and contributed to discussion. KX contributed to discussion. WJ supervised the study and revised the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Pre-publication history