RESEARCH ARTICLE

Association of *HS6ST3* gene polymorphisms with obesity and triglycerides: gene × gender interaction

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Abstract

The *heparan sulfate 6-O-sulfotransferase 3 (HS6ST3)* gene is involved in heparan sulphate and heparin metabolism, and has been reported to be associated with diabetic retinopathy in type 2 diabetes. We hypothesized that *HS6ST3* gene polymorphisms might play an important role in obesity and related phenotypes (such as triglycerides). We examined genetic associations of 117 single-nucleotide polymorphisms (SNPs) within the *HS6ST3* gene with obesity and triglycerides using two Caucasian samples: the Marshfield sample (1442 obesity cases and 2122 controls), and the Health aging and body composition (Health ABC) sample (305 cases and 1336 controls). Logistic regression analysis of obesity as a binary trait and linear regression analysis of triglycerides as a continuous trait, adjusted for age and sex, were performed using PLINK. Single marker analysis showed that six SNPs in the Marshfield sample and one SNP in the Health ABC sample were associated with obesity ($P < 0.05$). SNP rs535812 revealed a stronger association with obesity in meta-analysis of these two samples ($P = 0.0105$). The T–A haplotype from rs878950 and rs9525149 revealed significant association with obesity in the Marshfield sample ($P = 0.012$). Moreover, nine SNPs showed associations with triglycerides in the Marshfield sample ($P < 0.05$) and the best signal was rs1927796 ($P = 0.00858$). In addition, rs7331762 showed a strong gene × gender interaction ($P = 0.00956$) for obesity while rs1927796 showed a strong gene × gender interaction ($P = 0.000625$) for triglycerides in the Marshfield sample. These findings contribute new insights into the pathogenesis of obesity and triglycerides and demonstrate the importance of gender differences in the aetiology.

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Introduction

Obesity has become a global epidemic and contributes to the increasing burden of diabetes, cardiovascular disease, osteoarthritis, respiratory disease and a range of cancers (Flegal *et al.* 2007). In a recent report, the absolute number of individuals was projected to become a total of 2.16 billion for being overweight and 1.12 billion for being obese by 2030, respectively (Kelly *et al.* 2008). Obesity is typically measured clinically with the surrogate measure of body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. Individuals with a BMI ≥ 25 kg/m^2 are classified as being overweight, and those with a BMI ≥ 30 kg/m^2 are considered obese (Frayling *et al.* 2007). Obesity is highly heritable and arises from the interactions of multiple genes, environmental factors and behaviour. Family and twin studies have shown that genetic factors account for 40–70% of the population variation in obesity (Allison *et al.* 1996; Maes *et al.* 1997; Atwood *et al.* 2002). Triglycerides are fatty substances which are closely associated with cholesterol, another fatty substance. High triglycerides are an early warning signal for obesity and metabolic syndrome. Heritability estimates for cholesterol and triglycerides are 65 and 75% from twin study vs 42 and 37% from pedigree study (Hunt *et al.* 1989). Identifying genes and genetic variants associated with plasma triglyceride concentration will enrich our understanding of biochemical pathways involved in triacylglycerol (TAG)-rich lipoprotein metabolism, enabling identification of subjects with increased susceptibility to disordered metabolism, and development of therapeutic interventions to improve plasma triglycerides concentration and ameliorate heart disease risk (Johansen *et al.* 2011).

Heparan sulphate (HS) is a highly sulphated polysaccharide that can be found on the cell surface and extracellular matrix. HS interacts with a variety of proteins, such as growth factors, protease inhibitors, cytokines, lipoprotein

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lipase and viral envelope proteins, to play important roles in cell growth, cell differentiation, cell motility, blood coagulation, lipid metabolism and viral infection. Habuchi *et al.* (2000) cloned the gene *HS 6-O-sulfotransferase 3* (*HS6ST3*) at 13q32.1 and demonstrated that HS6ST3 showed 6-O-sulfotransferase activity against HS, N-sulphated heparosan, heparin and some HS derivatives. It has been reported that HS O-sulphotransferases catalyze the O-sulphation of the glucosamine and uronic acid residues of HS, thereby determining the binding sites for ligands necessary to improve biological functions such as the formation of morphogen gradients and growth factor signalling (Nagai *et al.* 2004). Studies have shown that the enzymes and proteins encoded by *HS6ST3* are involved in HS and heparin metabolism pathway (Torkamani *et al.* 2008; Jiang *et al.* 2011). Williams and Chen (2010) have reported that lipoproteins that persist in the bloodstream are contributors to obesity, type 2 diabetes, overnutrition and atherosclerotic vascular disease. Jiang *et al.* (2011) used cattle as an organism to investigate the association of these genes with the regulation of lipid metabolism. Their results showed that when a cell's heparin sulphate chain was degraded with heparinase, the cell would suffer from impaired lipoprotein uptake. They concluded that specific 6-O-sulphate groups must play an important role in lipoprotein binding and uptake. Since HS6T3 plays an important role in the heparin sulphate and heparin metabolism pathway, we hypothesize that *HS6T3* is associated with obesity and metabolic phenotypes. Recently, a novel SNP for *HS6ST3* was identified for the susceptibility of diabetic retinopathy in type 2 diabetes in a Taiwanese population using a case–control study (Huang *et al.* 2011). However, till now no study has been conducted focussing on obesity and metabolic phenotypes such as triglycerides.

Meta-analysis refers to the statistical synthesis of results from a series of studies. If an effect size is consistent across the series of studies, the meta-analysis procedures can be used to report that the effect is robust across the samples and also to estimate the magnitude of the effect more precisely that we could win with any of the studies alone. Meta-analysis of combined data proves to be a more powerful tool to improve the statistical power by increasing sample size (Borenstein *et al.* 2009; Guerra and Goldstein 2010). The aims of the present study were to investigate the possible associations of *HS6ST3* polymorphisms with obesity and triglycerides and to detect gene × gender interactions influencing obesity and triglycerides.

Materials and methods

Samples

The Marshfield sample: The Marshfield sample is from the publicly available data from 'A genome-wide association study on cataract and HDL in the Personalized Medicine Research Project Cohort—Study Accession: phs000170.v1.p1 (dbGaP). The primary goals of this project are to develop and validate electronic phenotyping algorithms, to accurately identify cases and controls while maintaining a positive predictive value (PPV) of >95%, and to conduct a genomewide association study that advances the understanding of two specific yet interrelated disease states, while simultaneously engaging the community in these research efforts. The details about these subjects are described elsewhere (McCarty *et al.* 2005, 2008). Genotyping data using the ILLUMINA Human660W-Quad_v1_A are available for 3564 individuals (1442 cases and 2122 controls and 2147 individuals with triglycerides).

The Health ABC sample: The 'Health aging and body composition' (Health ABC) study is the 'Whole genome association study of visceral adiposity in the health aging and body composition (Health ABC) study' (dbGaP Study Accession: phs000169.v1.p1) (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study_id=phs000169.v1.p1). It is a National Institute on Aging (NIA)-sponsored cohort study of the factors that contribute to incident disability and the decline in function of healthier older persons, with a particular emphasis on changes in body composition in old age. The key components of Health ABC include a baseline exam, annual follow-up clinical exams and phone contacts every six months to identify major health events and document functional status between clinic visits. The HABC dataset contains 1M Illumina Human SNPs for 1641 individuals (305 obese individuals and 1336 controls: 867 males and 764 females).

Statistical analysis

To deal with population stratification, the principal-component analysis (PCA) approach (Price *et al.* 2006) in HelixTree software (http://www.goldenhelix.com/SNP_Variation/HelixTree/index.html) was used to identify outlier individuals. Hundred and seventeen SNPs were available within the *HS6ST3* gene for both the samples. Logistic regression analysis of obesity as a binary trait, adjusted for age and sex, was performed using PLINK ver. 1.07 (Purcell *et al.* 2007). The asymptotic *P* values for this test were observed while the odds ratio (OR) and standard error (SE) of OR were estimated. For logistic regression, the additive model was applied. To test for association with triglycerides level as a quantitative trait, adjusted for age and sex, linear regression was performed by PLINK ver. 1.07 (Purcell *et al.* 2007) to obtain the regression coefficient and Wald test asymptotic *P* value. Hardy–Weinberg equilibrium (HWE) was tested for all the SNPs using Haploview software (MIT/Harvard Broad Institute, Cambridge, USA) (Barrett *et al.* 2005). Then, minor allele frequency (MAF) was determined for each SNP and the linkage disequilibrium (LD) structure was constructed using Haploview software. Haplotype analysis was performed for obesity using UNPHASED ver. 2.404 (Dudbridge 2008).

Meta-analysis: Both the Marshfield and the Health ABC samples used the Illumina (Illumina, San Diego, USA) genotyping platform. Results of obesity from the two samples were meta-analysed by combining the separate results (OR and SE of OR) into one meta-analysis of overall effect (meta-analysis for triglycerides was not available because the Health ABC sample did not have triglycerides variable). For meta-analysis of two datasets, the basic meta-analysis function in PLINK was applied. Fixed-effects meta-analysis *P* value and fixed-effects OR were estimated. The between-study heterogeneity was tested by the χ^2-based Cochrane's Q statistic (Higgins and Thompson 2002).

Gene × gender interaction: Logistic and linear models in PLINK were used to test for sex-specific associations and gene × gender interactions for obesity and triglycerides, respectively.

Results

Genotype quality control and descriptive statistics

All SNPs were in HWE in the controls ($P > 0.01$). Participant characteristics for two samples are presented in table 1. The mean values of BMI were 26.6 and 29.6 kg/m^2 for the two datasets, respectively. The mean value of triglycerides in the Marshfield sample was 143.3 (mg/dL).

Table 1. Characteristics of the Health ABC and Marshfield subjects.

Parameter	Health ABC	Marshfield
Number	1641	3564
Women (%)	764 (47%)	2089 (59%)
Obesity		
No	1336	2122
Yes	305	1442
Triglycerides (mg/dL)		
Mean ± SD	–	143.3 ± 61.9
Age (years)		
Mean ± SD	73.8 ± 2.85	66.3 ± 11.3
BMI (kg/m^2)		
Mean ± SD	26.6 ± 4.1	29.6 ± 5.8

Association with obesity

Single marker analysis showed that one SNP (rs9562057 with $P = 0.0174$) in the Health ABC sample and six SNPs in the Marshfield sample were associated with obesity ($P < 0.05$) (table 2). A more comprehensive list of SNPs (total 117 SNPs) is presented in table 1 in electronic supplementary material at http://www.ias.ac.in/jgenet/. The SNP rs878950 was most significantly associated with obesity ($P = 0.0138$) in the Marshfield sample. SNP rs535812 revealed a stronger association with obesity in meta-analysis of the two samples ($P = 0.0105$). All *P* values based on the *Q* statistic (Higgins and Thompson 2002) were larger than 0.05, which indicated that there was no heterogeneity for these seven SNPs between the Health ABC sample and the MARSHFIELD sample (table 2). The MAF for the same SNP of both datasets were identical while the association directions for the top seven SNPs were the same for both the datasets as revealed by OR values. The SNP rs9562057 in the Health ABC sample and six of seven SNPs in the Marshfield sample had empirical pointwise *P* values < 0.05 using a permutation procedure (table 2).

We identified haplotype blocks for 18 SNPs using Haploview including the most significantly associated SNPs in both samples. Figure 1 shows the LD (r^2) structure. The C–T haplotype from rs7331762 and rs9525147 and the T–A haplotype from rs878950 and rs9525149 revealed a significant association with obesity in the Marshfield sample ($P = 0.016$ and 0.012, respectively) (table 3).

Association with triglycerides in the Marshfield sample

Single marker analysis showed that nine SNPs were associated with triglycerides ($P < 0.05$) (table 4). The best signal was rs1927796 ($P = 0.00858$) and the second best SNP was rs1927801 ($P = 0.00955$). These two SNPs also revealed borderline associations with obesity ($P = 0.092$ and 0.0786,

Table 2. SNPs associated with obesity in the Health ABC and Marshfield samples.

SNP	Position	Allele[a]	P^b_{meta}	Q[c]	MAF[d]	OR[e]	P^f	EMP[g]	MAF[h]	OR[i]	P^j	EMP[k]
rs9562057	95695857	T	0.622	0.01	0.11	1.55	0.0174	0.0189	0.11	0.89	0.157	0.168
rs878950	95652682	T	0.0205	0.369	0.46	1.03	0.769	0.748	0.46	1.13	0.0138	0.0119
rs9525147	95645616	T	0.0278	0.347	0.46	1.02	0.831	0.811	0.46	1.12	0.0173	0.0129
rs535812	95563620	G	0.0105	0.807	0.36	1.10	0.311	0.309	0.36	1.13	0.0188	0.0179
rs7331762	95643558	T	0.366	0.213	0.48	1.03	0.742	0.756	0.49	0.89	0.0232	0.0239
rs9525149	95653783	G	0.0592	0.48	0.47	0.98	0.825	0.846	0.47	0.91	0.0433	0.0398
rs17767562	96073933	C	0.0703	0.389	0.44	0.99	0.943	0.926	0.44	0.91	0.0434	0.0589

[a]Minor allele; [b]*P* value for the meta-analysis; [c]*P* value for Cochrane's Q statistic; [d]minor allele frequency in the Health ABC sample; [e]odds ratio for the Health ABC sample; [f]*P* value for the Health ABC sample based on logistic regression; [g]empirical *P* value for the Health ABC sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK; [h]minor allele frequency in the Marshfield sample; [i]odds ratio for the Marshfield sample; [j]*P* value for the Marshfield sample based on logistic regression; [k]empirical *P* value for the Marshfield sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK.

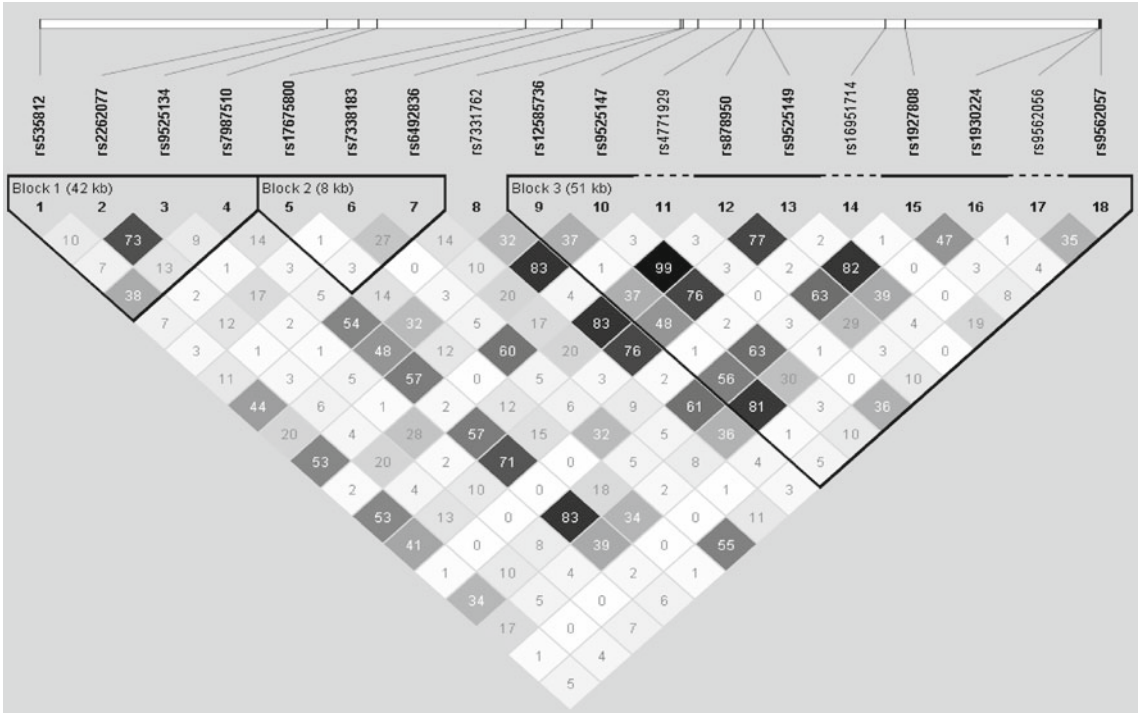

Figure 1. Linkage disequilibrium structure (r^2) within the *HS6ST3* gene including rs9562057 and rs878950 and rs9525147.

Table 3. Haplotype analysis of *HT6ST3* with obesity in the Marshfield sample based on UNPHASED.

Haplotype		Marshfield sample			
		Case[a]	Control[b]	OR[c]	P[d]
rs7331762	rs9525147				
C	C	118 (5%)	190 (4%)	1	0.427
C	T	1421 (49%)	1966 (46%)	1.16	0.016
T	C	1345 (46%)	2083 (49%)	1.04	0.0389
rs878950	rs9525149				
G	A	168 (6%)	276 (7%)	1	0.241
G	G	1295 (45%)	2002 (47%)	1.06	0.0545
T	A	1421 (49%)	1961 (46%)	1.19	0.0122

[a]Haplotype number and frequency in cases; [b]haplotype number and frequency in controls; [c]odds ratio based on standard case–control haplotype analysis; [d]P value based on standard case–control haplotype analysis.

Table 4. SNPs associated with obesity and triglycerides in the Marshfield sample.

SNP	Position	Allele[a]	MAF[b]	OR[c]	P[d]	EMP[e]	B[f]	P[g]	EMP[h]
rs1927796	95716834	T	0.47	0.92	0.092	0.107	−5.328	0.00858	0.0119
rs1927801	95703618	C	0.47	0.92	0.0786	0.0909	−5.26	0.00955	0.0149
rs9562056	95695709	A	0.04	0.87	0.300	0.279	−12.26	0.0169	0.0219
rs7322488	95714635	C	0.04	0.86	0.224	0.217	−11.75	0.0205	0.0279
rs12561187	95734967	A	0.04	0.85	0.197	0.189	−11.22	0.0254	0.0329
rs12583999	95789919	A	0.25	0.95	0.349	0.355	−5.12	0.0264	0.0259
rs9556553	95754094	C	0.04	0.88	0.296	0.291	−10.27	0.0366	0.0419
rs7328493	95798499	G	0.33	0.92	0.132	0.139	−4.36	0.0413	0.0439
rs7325688	95976260	T	0.10	0.99	0.95	0.942	−6.69	0.0479	0.0519

[a]Minor allele; [b]minor allele frequency; [c]odds ratio; [d]P value for obesity based on logistic regression; [e]empirical P value for the Marshfield sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK; [f]regression coefficient for triglycerides; [g]P value for triglycerides based on linear regression; [h]empirical P value for the Marshfield sample generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK.

Table 5. Gene × gender interaction for obesity in the Marshfield samples.

	SNP	Position	Allele[a]	MAF[b]	OR_int[c]	P[d]	OR_all[e]	P[f]	OR_male[g]	P[h]	OR_female[i]	P[j]
1	rs7331762	95643558	T	0.49	0.93	0.00956	0.89	0.0232	0.88	0.0893	0.91	0.137
2	rs9525149	95653783	G	0.47	0.94	0.0173	0.91	0.0433	0.89	0.128	0.92	0.194
3	rs17767562	96073933	C	0.44	0.94	0.0265	0.90	0.0434	0.86	0.0513	0.94	0.358
4	rs732121	95897355	G	0.06	0.87	0.031	0.87	0.19	1.22	0.239	0.69	0.011
5	rs732123	95897048	G	0.05	0.86	0.0333	0.84	0.142	1.15	0.467	0.69	0.0187
6	rs11069237	95807454	G	0.49	0.94	0.0371	0.92	0.0755	0.86	0.0506	0.96	0.54
7	rs7987510	95605772	C	0.42	0.94	0.0389	0.92	0.117	0.93	0.32	0.93	0.242
8	rs1927801	95703618	C	0.47	0.94	0.0389	0.92	0.0786	0.87	0.0765	0.95	0.447
9	rs1927796	95716834	T	0.47	0.95	0.0429	0.92	0.092	0.88	0.0972	0.95	0.447
10	rs1888977	95825574	T	0.46	0.95	0.0496	0.93	0.133	0.91	0.248	0.94	0.372

[a]Minor allele; [b]minor allele frequency; [c]odds ratio for the gene × gender interaction; [d]P value for interaction based on logistic regression; [e]odds ratio for the whole sample; [f]P value for the whole sample based on logistic regression; [g]odds ratio for the males; [h]P value for the males based on logistic regression; [i]odds ratio for the females; [j]P value for the females based on logistic regression.

Table 6. Gene × gender interaction for triglycerides in the Marshfield samples.

	SNP	Position	Allele[a]	MAF[b]	β_int[c]	P[d]	β_all[e]	P[f]	β_male[g]	P[h]	β_female[i]	P[j]
1	rs1927796	95716834	T	0.47	−3.99	0.000625	−5.33	0.00858	−9.72	0.0025	−2.03	0.4365
2	rs1927801	95703618	C	0.47	−3.91	0.000807	−5.26	0.00955	−9.97	0.00199	−1.75	0.501
3	rs7331762	95643558	T	0.49	−3.69	0.00145	−3.45	0.0872	−5.73	0.0695	−1.64	0.53
4	rs11069237	95807454	G	0.49	−3.54	0.00202	−3.74	0.0612	−5.95	0.0533	−1.9	0.469
5	rs9634489	95847005	G	0.49	−3.45	0.00229	−2.62	0.186	−3.28	0.279	−2.04	0.435
6	rs9525149	95653783	G	0.47	−3.51	0.00242	−3.75	0.092	−7.53	0.0172	−0.81	0.753
7	rs9562056	95695709	A	0.04	−9.03	0.0042	−12.26	0.0169	−12.15	0.135	−12.49	0.0579
8	rs7325688	95976260	T	0.10	−5.87	0.00543	−6.69	0.0479	−3.67	0.478	−9.29	0.0376
9	rs7322488	95714635	C	0.04	−8.65	0.00576	−11.75	0.0205	−11.67	0.142	−11.95	0.0684
10	rs9300342	95749951	A	0.45	−3.24	0.00609	−3.41	0.0923	−6.32	0.0473	−1.12	0.669
11	rs9556582	95838532	A	0.46	−3.18	0.00638	−3.01	0.137	−5.84	0.0632	−0.7	0.791
12	rs3892845	95956287	T	0.10	−5.75	0.0068	−6.62	0.0506	−3.88	0.45	−9.06	0.0441
13	rs12561187	95734967	A	0.04	−8.33	0.0071	−11.22	0.0254	−11.85	0.134	−10.85	0.0934
14	rs979231	95859562	G	0.46	−3.09	0.00747	−2.49	0.214	−3.92	0.205	−1.29	0.622
15	rs1888977	95825574	T	0.46	−3.12	0.00793	−3.30	0.103	−6.71	0.0351	−0.62	0.814
16	rs7987510	95605772	C	0.42	−3.16	0.00842	−3.24	0.111	−6.77	0.032	−0.35	0.896

[a]Minor allele; [b]minor allele frequency; [c]regression coefficient for the gene × gender interaction; [d]P value for interaction based on linear regression; [e]regression coefficient for the whole sample; [f]P value for the whole sample based on linear regression; [g]regression coefficient for the males; [h]P value for the males based on linear regression; [i]regression coefficient for the females; [j]P value for the females based on linear regression.

respectively). Eight of nine SNPs for the triglycerides had empirical pointwise P values < 0.05 using a permutation procedure (table 4).

Gene × gender interaction in the Marshfield sample

Table 5 lists the top 10 findings with P values < 0.05 for the gene × gender interactions influencing obesity. The SNP rs7331762 showed the strongest gene × gender interaction ($P = 0.00956$) for obesity. Of these 10 SNPs, two SNPs showed associations with obesity in the female sample and three showed associations in the whole sample but no SNP revealed associations in the male sample. Table 6 lists the top 16 findings with P values < 0.01 for the gene × gender interactions influencing triglycerides. rs1927796 showed the strongest gene × gender interaction ($P = 0.000625$) for triglycerides. Of these 16 SNPs, six SNPs showed associations with triglycerides in the male sample and six SNPs showed associations in the whole sample while just two SNPs revealed associations in the female sample.

Discussion

In this study we found statistically significant associations of several SNPs within *HS6ST3* gene with obesity and triglycerides. Meta-analysis and haplotype analysis further supported the single marker analysis results. Further, we found several SNPs interacted with gender influencing the obesity and triglycerides. To our knowledge, this is the first study to investigate associations of *HS6ST3* gene polymorphisms with obesity and triglycerides and to detect gender differences in the associations of *HS6ST3* gene polymorphisms with obesity and triglycerides.

It has been reported that HSs exert critical regulatory actions on many proteins, including growth factors, protease inhibitors, cytokines and lipoprotein lipase, therefore playing roles in cell growth, cell differentiation, cell motility, blood coagulation and lipid metabolism, and are essential for normal development (e.g., Habuchi *et al.* 2000; Ford-Perriss *et al.* 2002; Nagai *et al.* 2004; Torkamani *et al.* 2008; Jiang *et al.* 2011). Animal models such as *Drosophila* and mice have also shown that *HS6ST3* is involved in both limb bud development and tracheal branching (Kamimura *et al.* 2001; Nogami *et al.* 2004). A previous genomewide association study of diabetic retinopathy in type 2 diabetes identified a novel SNP (rs2038823 with $P = 4.68 \times 10^{-11}$) within *HS6ST3* gene in a Taiwanese population using a case–control study (Huang *et al.* 2011). In the present study, we reported the first study of associations of *HS6ST3* gene polymorphisms with obesity and triglycerides. We could not find associations of rs2038823 with obesity or triglycerides. However, we found several SNPs within this gene associated with obesity and triglycerides. Such differences may lie in either the different outcomes used, or genetic heterogeneity in different ethnic populations.

Further, our results revealed gender differences in the associations of *HS6ST3* gene polymorphisms with obesity and triglycerides. Gender-specific associations with obesity have been previously reported in the associations of other genes with obesity. For example, a positive association between obesity and the Glu27 genetic variant in the *beta-2-adrenoceptor* gene existed in females, whereas in males there was a negative correlation between Glu27 and obesity (Hellström *et al.* 1999). A *beta(3)-adrenergic receptor* gene variant was associated with upper body obesity only in obese Japanese–American men but not in women (Kawamura *et al.* 2001). Corbalán *et al.* (2002) showed that the 27Glu allele of the *ADRB2* gene appeared to be a risk factor for abdominal obesity among male subjects, especially among those with lower HDL-cholesterol levels. Another study suggested that the Glu27 allele of the *beta-2-adrenoceptor* gene might be a risk factor for the accumulation of visceral fat in men but not in women (González Sánchez *et al.* 2003). In European general populations, the combined effects of common polymorphisms in *FTO* and *MC4R* were additive, predictive of obesity and T2D, and might be influenced by interactions with physical activity levels and gender, respectively (Cauchi *et al.* 2009).

There are several studies revealing gender-specific associations with triglycerides in some genes. Associations of the acid phosphatase (*ACP1*) genotypes were found to be significantly associated with total cholesterol and triglyceride levels in the obese women only (Bottini *et al.* 2002) while polymorphisms in the *APOA5* gene were associated with triglyceride levels in Chinese men but not in Chinese women (Baum *et al.* 2003). Another study showed significant gender × genotype (*apoA-V* gene variants) interactions for fasting TG with a greater impact of genotype in males (Olano-Martin *et al.* 2008). In addition, *APOC3*-482TT genotype has been reported to be independently associated with elevated fasting triglyceride concentrations in obese men (Coban *et al.* 2011).

Obesity has become a global epidemic and contributes to the increasing burden of diabetes cardiovascular disease, osteoarthritis, respiratory disease and a range of cancers (Flegal *et al.* 2007). Obesity has a direct link with high levels of triglycerides. It is known that there is a correlation between fatness and triglycerides while obesity is associated with increased tissue triglyceride content (Albrink *et al.* 1980; Koyama *et al.* 1997). Animal model also showed that islets of hyperinsulinaemic obese rats have an extremely high triglyceride content compared with normal littermates (Lee *et al.* 1994). Recently, it has been suggested that obesity may be defined as excess storage of inert triglycerides (Sørensen 2011). *APOA5* gene variation demonstrated a gene × nutrient interaction for obesity (Corella *et al.* 2007) and also provided evidence for a gene × diet interaction for a second outcome, that of plasma TG (Sánchez-Moreno *et al.* 2011). It has been suggested that it is potentially useful for a nutrigenomic approach in optimizing a dietary intervention for the prevention of obesity and cardiovascular disease based on fat intake recommendations tailored to the individual genotype (Sánchez-Moreno *et al.* 2011).

There are a number of strengths in this study. First, our sample size was relatively large for this type of study and was relatively ethnically homogeneous. Second, we simultaneously performed a single marker analysis, meta-analysis and haplotype analysis. Third, we detected gene × gender interactions for obesity and also for triglycerides. We also realized some limitations in this study. First, our current findings might be spurious or subject to type I error. Second, we only had two samples for the meta-analysis of obesity. Therefore, these findings need to be replicated in additional samples.

Conclusions

In the present study, we report the first association study of *HS6ST3* gene polymorphisms with obesity and triglycerides. Our results not only demonstrate that *HS6ST3* variants are associated with obesity and triglycerides but also provide genetic basis for gender differences in obesity and triglycerides. These findings may serve as a resource for replication in other populations to elucidate the potential role of these genetic variants. Future functional study of this gene may help to better characterize the genetic architecture of obesity and triglycerides.

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