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Replication and Identification of Novel Variants at *TCF7L2* Associated with Type 2 Diabetes in Hong Kong Chinese

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Objective: Variations at a large linkage disequilibrium (LD) block of transcription factor 7-like 2 gene (*TCF7L2*) were reported to be associated with type 2 diabetes (T2D) in Icelandic, Danish and European-American populations and further replicated in other populations of European, African, and Asian ancestries. However, data for Chinese and comprehensive survey of the whole gene are lacking.

Design: We attempted to examine 22 tagging single-nucleotide polymorphisms (SNPs) spanning across the *TCF7L2* gene for association with T2D in Hong Kong Chinese. We first studied a case-control sample involving 433 hospital cases with familial early-onset T2D and 419 normal controls and further studied the associated SNPs in 450 members of 142 diabetic families.

Results: Two of the previously reported risk alleles at rs11196205 (C) and rs7903146 (T) were rare in Chinese (0.013 and 0.024, respectively, in controls). Rs11196205 was associated with T2D [odds ratio (OR) [95% confidence interval (CI)] = 2.11 (1.04–4.26)], whereas the association for rs7903146 [OR (95% CI) = 1.27 (0.71–2.29)] was not significant in the case-control sample. Interestingly, another SNP (rs11196218 G allele) located in adjacent LD block conferred independent risk for T2D [OR (95%CI) =1.43 (1.14–1.79)] and contributed high-population attributable risk of 42%. The association finding of rs11196218 and its haplotype for T2D was also replicated in the family sample ($P < 0.05$).

Conclusions: Our results are consistent with others' findings that variations at *TCF7L2* contribute to T2D, including Chinese. The presence of association signals spanning several LD blocks warrants further examination of extended regions to reveal the causal variant(s) for this important T2D gene. **(*J Clin Endocrinol Metab* 92: 3733–3737, 2007)**

TRANSCRIPTION FACTOR 7-LIKE 2 (TCF7L2) has recently been implicated in the pathogenesis of type 2 diabetes (T2D) through regulation of pancreatic β-cell insulin secretion. The *TCF7L2* gene at chromosome 10q25 was first reported to be associated with T2D in Icelandic, Danish, and European-American populations (1). The associated single-nucleotide polymorphisms (SNPs) were clustered within a single large linkage disequilibrium (LD) block of 92.1kb spanning intron 3 and intron 4 of *TCF7L2* and were subsequently replicated in populations of European, African, and Asian ancestries (2–11). The at-risk alleles were likely associated with lower anthropometric index (12, 13) and lower insulin secretion capacity in healthy and/or diabetic subjects (2, 3, 9, 13–16).

Whereas most replication studies focus on the SNPs within a single LD block, Lehman *et al.* recently found the association signals extended to 5′ and 3′ of the reported LD block in Mexican-Americans (8). In this study, we attempted to study tagging SNPs spanning across the *TCF7L2* gene to confirm previous associations as well as to detect novel regions for association with T2D. We studied 22 SNPs in a case-control sample from Hong Kong including 433 hospital cases with familial early-onset type 2 diabetes and 419 normal controls. The associated SNPs were further replicated in 450 members of 142 diabetic families recruited from the Hong Kong Family Diabetes Study.

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Abbreviations: BMI, Body mass index; CHB, Han Chinese; CI, confidence interval; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA, homeostasis model assessment; ISI, insulin sensitivity index; LD, linkage disequilibrium; MAF, minor allele frequency; OGTT, oral glucose tolerance test; OR, odds ratio; PAR, population-attributable risk; SNP, single-nucleotide polymorphism; TCF7L2, transcription factor 7-like 2; T2D, type 2 diabetes.

Subjects and Methods

Subjects

All subjects were of southern Han Chinese ancestry residing in Hong Kong. The study included individuals from three independent samples. The first sample (cases) consisted of 433 unrelated T2D patients selected from the Hong Kong Diabetes Registry (17). All patients were early-onset (diagnosed ≤ 40 yr) with positive family history of diabetes in first-degree relatives. The second sample (controls) consisted of 419 normal control subjects [fasting plasma glucose (FPG) < 6.1 mmol/liter] recruited from the general population participating in a community-based cardiovascular risk screening program as well as hospital staff. The third sample (families) included 142 families consisting of probands, siblings, and parents (450 subjects, 266 diabetics, average family size 3.2 ± 1.1) recruited from the Hong Kong Family Diabetes Study. The details of ascertainment, exclusion criteria, and phenotyping of the families are described elsewhere (18). The clinical characteristics of subjects in the three samples are summarized in Table 1. Informed consent was obtained for each participating subject. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong.

TABLE 1. Clinical characteristics of study populations

	Controls (n = 419)	Diabetics (n = 433)	Family (n = 450)
Male (%)	40	38	39
Age (yr)	40.6 ± 10.4	39.4 ± 8.5	46.5 ± 14.5
Duration of diabetes (yr)		8.1 ± 7.6	6.6 ± 7.6
BMI (kg/m^2)	22.5 ± 3.2	25.8 ± 4.7	26.5 ± 4.4
Diabetes (%)	0	100	59

Clinical studies

All subjects underwent detailed clinical investigation as described previously (17, 19). Obesity was defined as body mass index (BMI) 25 kg/m^2 or greater using the Asian criteria (20). A fasting blood sample was collected for measurement of plasma glucose and insulin (FPI). All family members and 295 controls who had no history of diabetes underwent a 75-g oral glucose tolerance test (OGTT). Three fasting blood samples collected at 5-min intervals were assessed for mean FPG and FPI. Blood samples were also collected at 15, 30, 60, and 120 min during OGTT for measurement of plasma glucose and insulin. Using the homeostasis model assessment (HOMA), HOMA insulin resistance index was assessed as FPI (milliunits per liter) × FPG (millimoles per liter)/22.5, and HOMA of β-cell function was assessed as FPI × 20/(FPG − 3.5) (21). Using the OGTT data, insulinogenic index, a measure of early phase insulin secretion, was assessed as (insulin 30 min − 0 min)/(glucose 30 min − 0 min) (22). Data were discarded if glucose or insulin levels at 30 min were less than that of the fasting levels. Insulin sensitivity index (ISI) was assessed as 10,000/square root of [(FPG × FPI) × (mean glucose × mean insulin during OGTT)]. Insulin disposition index was assessed as ISI × insulinogenic index/100 (23).

Genotyping

We genotyped 22 SNPs that span 2 kb upstream and downstream of *TCF7L2* [chromosome 10: 114,698,200 to 114,918,057 bp; HapMap release 20 (Jan. 2006), NCBI Build 35; National Center for Biotechnology Information, Bethesda, MD]. Twenty tagging SNPs were selected from the Phase II HapMap Han Chinese in Beijing, China (CHB) population using Haploview (version 3.32) based on r^2 greater than 0.64 and minor allele frequency (MAF) 0.05 or greater (24). These tagging SNPs were able to capture 49 of 58 (84%) common SNPs at r^2 greater than 0.64 or 71% of common SNPs at r^2 greater than 0.8. Two additional SNPs (rs7903146 and rs11196205) were also genotyped for replication study (1) despite their low frequencies in the HapMap CHB population. All SNPs were genotyped using primer extension of multiplex products with detection

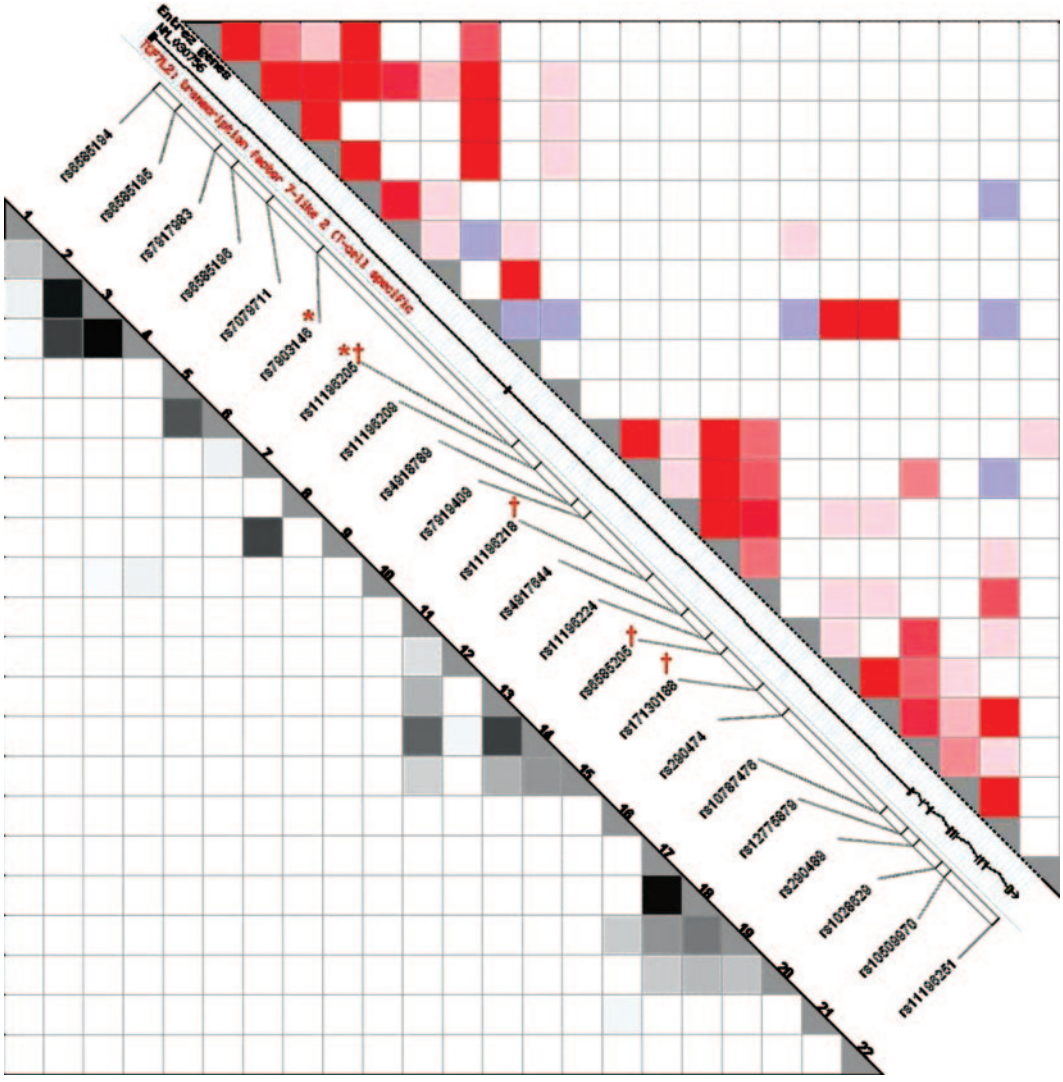

FIG. 1. Structure of *TCF7L2* gene and the location of SNPs studied. Pairwise LDs among SNPs are indicated in *upper block* (D′) and *lower block* (r^2). *Increased color intensity* represents increased degree of LD as implemented in Haploview. *, SNPs showing significant association to T2D in study by Grant *et al.* (1). †, SNPs showing significant association to T2D in the present case-control study.

TABLE 2. Allelic association for T2D for 22 tagging SNPs in the *TCF7L2* gene in case-control sample

SNP	Chromosome 10 position	*TCF7L2* region	Major/minor allele	Minor allele frequency		OR (95% CI)	*P*
				Controls (n = 419)	Diabetics (n = 433)		
rs6585194	114707461	Intron 3	C/G	0.302	0.288	0.93 (0.75–1.16)	0.536
rs6585195	114712944	Intron 3	C/G	0.352	0.372	1.09 (0.89–1.34)	0.41
rs7917983	114722872	Intron 3	C/T	0.352	0.308	0.82 (0.67–1.01)	0.06
rs6585196	114727040	Intron 3	T/C	0.330	0.305	0.89 (0.72–1.09)	0.264
rs7079711	114735778	Intron 3	G/A	0.023	0.034	1.51 (0.84–2.7)	0.168
rs7903146	114748339	Intron 3	C/T	0.024	0.030	1.27 (0.71–2.29)	0.424
rs11196205	**114797037**	**Intron 4**	**G/C**	**0.013**	**0.028**	**2.11 (1.04–4.26)**	**0.038**
rs11196209	114802717	Intron 4	G/A	0.025	0.020	0.79 (0.41–1.5)	0.47
rs4918789	114811797	Intron 4	T/G	0.019	0.034	1.8 (0.98–3.31)	0.06
rs7919409	114814966	Intron 4	T/C	0.254	0.262	1.05 (0.84–1.3)	0.687
rs11196218	**114830484**	**Intron 4**	**G/A**	**0.285**	**0.219**	**0.7 (0.56–0.88)**	**0.002**
rs4917644	114839389	Intron 4	C/T	0.063	0.047	0.74 (0.48–1.12)	0.157
rs11196224	114845387	Intron 4	C/T	0.281	0.265	0.92 (0.74–1.14)	0.454
rs6585205	**114849154**	**Intron 4**	**G/T**	**0.441**	**0.379**	**0.78 (0.64–0.94)**	**0.01**
rs17130188	**114858152**	**Intron 4**	**T/C**	**0.497**	**0.561**	**1.29 (1.06–1.57)**	**0.011**
rs290474	114864363	Intron 4	G/A	0.102	0.128	1.3 (0.96–1.76)	0.095
rs10787476	114888904	Intron 4	A/C	0.214	0.249	1.21 (0.97–1.52)	0.095
rs12775879	114894191	Intron 4	T/G	0.222	0.242	1.12 (0.89–1.4)	0.336
rs290489	114897045	Intron 4	G/A	0.284	0.306	1.11 (0.9–1.37)	0.312
rs1028629	114902646	Intron 10	C/T	0.179	0.166	0.91 (0.71–1.17)	0.467
rs10509970	114904903	Intron 10	T/G	0.037	0.048	1.31 (0.81–2.1)	0.27
rs11196251	114916780	3′ to gene	C/T	0.354	0.374	1.09 (0.89–1.33)	0.406

Chromosome position and allele nomenclature are indicated using NCBI dbSNP build 35. OR and 95% CI are shown for T2D association respective to the minor allele. SNPs with significant association ($P < 0.05$) were in *bold*.

by matrix-assisted laser desorption ionization-time of flight mass spectroscopy using a MassARRAY platform (Sequenom, San Diego, CA). The genotyping was performed by the Genome Research Centre at the University of Hong Kong. The overall genotype call rate was 97%, and the concordance rate based on 108 blind duplicate comparisons for each SNP was 99.6%. There was no significant departure from Hardy-Weinberg equilibrium for all SNPs in the normal controls ($P > 0.05$) as assessed by χ^2 test. Mendelian inconsistencies were identified and removed in 0.03% of the family data using PEDCHECK (version 1.1; http://watson.hgen.pitt.edu/register/docs/pedcheck.html) (25).

Statistical analyses

Continuous data were transformed by natural logarithm if necessary and expressed as mean ± SD or geometric mean [95% confidence intervals (CIs)]. Allele and genotype frequencies for cases and controls were compared using χ^2 test. Odds ratio (OR) with 95% CI are presented. Haplotypes with frequencies greater than 5% in case-control study were compared using haplotype-specific test implemented in Haploview (24). Logistic regression for the four associated SNPs with T2D status was performed to assess independence of effect on T2D under an additive genetic model (except rs11196205 under a dominant model). Breslow-Day test was performed to assess homogeneity of ORs in subset analyses. For the family study, FBAT (version 1.7.2; Department of Biostatistics, Department of Environmental Health, Harvard School of Public Health; http://www.biostat.harvard.edu/~fbat/default.html) (26) was used to test for the association between SNPs or haplotypes and T2D under an additive genetic model with the −e option, which empirically estimated the variance. Quantitative traits were compared for SNPs under an additive model by linear regression with or without adjustment for age and gender. Population-attributable risk (PAR) was calculated as PAR = (X − 1)/X. Assuming a multiplicative model, $X = (1 - f)^2 + 2f(1 - f)\gamma + f^2\gamma^2$, where γ is the estimated OR and f is the frequency of risk allele. All statistical tests were performed by SAS (version 9.1; SAS Institute, Cary, NC) unless specified otherwise. A $P < 0.05$ was considered significant (two tailed). Given the presence of LD among the SNPs, 10,000 permutations of case-control labels were used to assess empirical *P* values for multiple allelic tests using Haploview.

Results

Case-control association

We genotyped 22 tagging SNPs spanning across *TCF7L2* as shown in Fig. 1. Previous study demonstrated that T2D-associated SNPs were located within a 92.1-kb LD block (chromosome 10: 114,723–114,815 kb, NCBI Build 35) (1). Whereas the SNPs in this block are relatively common in Utah residents with ancestry from Northern and Western Europe and Yoruba in Ibadan, Nigeria populations from HapMap, they are relatively rare (frequencies < 5%) in the CHB population, possibly due to positive selection at this region (27). We genotyped two SNPs (rs7903146 and rs11196205) within this block and found they were rare in our controls (MAF = 0.024 and 0.013, respectively), consistent with the HapMap CHB and Japanese populations (MAF = 0.02–0.04 and 0.03–0.05, respectively) (5, 6).

Table 2 summarizes the results of case-control allelic association for T2D with 22 tagging SNPs for *TCF7L2*. Whereas the previously reported at-risk C allele of rs11196205 was significantly associated with increased risk for T2D (OR 2.11, 95% CI 1.04–4.26), the T allele of rs7903146 was not significantly associated with T2D (OR 1.27, 95% CI 0.71–2.29). Interestingly, three additional common SNPs (rs11196218, rs6585205, and rs17130188) at intron 4 in adjacent LD blocks also demonstrated significant association to T2D (OR 1.29–1.43, $P = 0.002$–0.011, Table 2). However, only rs11196218 remained significant (empirical $P = 0.044$) after correction for multiple testing of 22 SNPs by permutations. Haplotype analyses of the three associated common SNPs (rs11196218, rs6585205, and rs17130188) revealed similar effect size, compared with the single SNP associations (Table 3). Only haplotypes constructed from at-risk (GGC) and protective (ATT) alleles conferred increased (OR

TABLE 3. Haplotype association of three associated SNPs (rs11196218, rs6585205, and rs17130188) for T2D in case-control sample

Haplotype	Frequency in controls	Frequency in diabetics	OR (95% CI)	*P*
GGC	0.400	0.476	1.36 (1.12–1.65)	0.002
ATT	0.226	0.170	0.70 (0.55–0.89)	0.004
GGT	0.153	0.140	0.90 (0.69–1.17)	0.433
GTT	0.128	0.137	1.09 (0.82–1.44)	0.559

Common haplotypes (frequency > 0.05) were tested using Haploview. GGC and ATT are constructed from the risk and protective alleles for rs11196218, rs6585205, and rs17130188, respectively.

1.36, 95% CI 1.12–1.65) and decreased risk (OR 0.70, 95% CI 0.55–0.89), respectively, for T2D. Logistic regression of T2D with all four associated SNPs showed that rs11196218 G allele and rs11196205 C allele tended to confer independent risk for T2D (adjusted OR 1.45 and 1.96, $P = 0.022$ and 0.096, respectively) whereas the association with rs6585205 and rs17130188 was not significant after adjustment ($P = 0.962$ and 0.306, respectively). We further examined the effects of gender and obesity status on the association results for the two independent associated SNPs rs11196218 and rs11196205. We found no significant heterogeneity of ORs between men and women [OR (95% CI) = 1.67 (1.17–2.37) *vs.* 1.27 (0.94–1.71) for rs11196218; 1.57 (0.67–3.68) *vs.* 4.69 (1.02–21.5) for rs11196205]. We also found no significant heterogeneity of ORs by comparing nonobese control subjects with either nonobese or obese diabetic patients [OR (95% CI) = 1.47 (1.09–1.98) *vs.* 1.32 (0.99–1.76) for rs11196218 and 2.39 (1.00–5.75) *vs.* 2.22 (0.92–5.34) for rs11196205] (supplementary Table 1, published as supplemental data on The Endocrine Society's Journals Online Web site at http://endo.endojournals.org). The ORs for these two SNPs were also similar before and after adjustment for BMI by logistic regression (data not shown).

Family-based association

We assessed the evidence of association of *TCF7L2* SNPs and haplotypes with T2D in our families using FBAT (Table 4). rs11196205 was too rare and ignored for analysis. Two of the three risk alleles in the case-control studies were also replicated or with trend of replication for association with T2D in the family study ($P = 0.041$ for rs11196218, $P = 0.094$ for rs6585205). Haplotype analysis with rs11196218 and rs6585205 showed similar results with the AT haplotype conferred protective effect for T2D ($P = 0.029$).

Metabolic trait association in normal controls

We also examined the association of the two significant SNPs (rs11196205 and rs11196218) with obesity index (as measured by BMI), insulin sensitivity (HOMA insulin resistance index, ISI), and insulin secretion (HOMA of β-cell function, insulinogenic index, insulin disposition index) at fasting or postprandial status. No association was observed for any of these metabolic traits with the two SNPs with or without adjustment for age and gender effects (supplemental Table 2).

Discussion

In the present study, we replicated previous findings of association of SNP (rs11196205) within a 92.1-kb LD block of *TCF7L2* with T2D using both case-control and family samples in our Chinese population. We further identified an additional SNP (rs11196218) downstream of the rs11196205 containing LD block that independently confer the risk for T2D (supplemental Fig. 1, published as supplemental data on The Endocrine Society's Journals Online web site at http://endo.endojournals.org).

In contrast to populations of European and African ancestries, SNPs within the large LD block with reported associations for rs11196205 (supplementary Figure 1) were rare in Chinese. Two recent case-control studies on more than 2000 Japanese subjects investigated SNPs within this LD block and found trend or significant association of rs11196205 and rs7903146 to T2D (5, 6). Notably the frequencies as well as the effect sizes of risk alleles for rs11196205 (C) and rs7903146 (T) in our Chinese population (OR = 2.11 and 1.27, respectively; Table 1) were consistent with findings from the Japanese studies (OR 1.21–1.37 and 1.30–1.69, respectively) (5, 6). Assuming a risk allele frequency of 0.04 and genotypic relative risk of 1.5 in multiplicative model using the Japanese data for rs7903146 (5, 6), 1650 case-control samples will be required to attain 80% power at α-level of 0.05 (28). The nonsignificant finding of rs7903146 in this study was probably due to insufficient power. In addition, the low risk allele frequency also led to the lower PAR of rs11196205 (3%) in our population, compared with European populations (PAR = 17–28%) (1). On the other hand, an additional SNP at 3′ of rs11196205, rs11196218 with higher risk allele frequency of 0.72 (Table 1), is likely to have higher impact on T2D in Chinese (PAR = 42%). A recent study in Mexican-Americans found that additional SNPs at 5′ and 3′ of the LD block also showed independent association to T2D (8).

We did not observe any association of the two T2D-related SNPs (rs11196205 and rs11196218) with the obesity, insulin sensitivity, and secretion traits in our normal controls (supplementary Table 2), as found in some studies (2, 3, 9, 12–15). Assuming the effect size observed from 995 Europeans on the insulinogenic index, which indicates early-phase insulin secretion (9), and assume a risk allele frequency of 0.05 for rs11196205 using data from the Japanese studies (5, 6), 28,900 samples will be required to attain 80% power at α-level of 0.05 using ANOVA

TABLE 4. Association of *TCF7L2* SNPs and haplotypes with T2D in 142 families using FBAT with the additive genetic model

Marker	Allele/haplotype frequency	Direction of transmission	*P*
rs11196218	G: 0.701	Increased	0.041
rs6585205	G: 0.554	Increased	0.094
rs17130188	C: 0.545	Increased	0.253
Haplotype			
rs11196218, rs6585205	GG: 0.569	Increased	0.154
	AT: 0.247	Decreased	0.029
	GT: 0.172	Increased	0.414

(29). This may partly explain the failure to detect quantitative traits association in our Chinese population.

Collectively, our data replicate previous findings by Grant *et al.* (1) and others and suggest that the causal variant(s) that confer risk for T2D in different populations including Chinese may reside within or adjacent to the originally reported LD block. Further investigation of more regions at this gene is warranted to elucidate the causal variants for T2D in this and other populations.

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