Brief Genetics Report

Association of Transcription Factor 7-Like 2 (*TCF7L2*) Variants With Type 2 Diabetes in a Finnish Sample

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Transcription factor 7-like 2 (*TCF7L2*) is part of the Wnt signaling pathway. Genetic variants within *TCF7L2* on chromosome 10q were recently reported to be associated with type 2 diabetes in Icelandic, Danish, and American (U.S.) samples. We previously observed a modest logarithm of odds score of 0.61 on chromosome 10q, ~1 Mb from *TCF7L2*, in the Finland-United States Investigation of NIDDM Genetics study. We tested the five associated *TCF7L2* single nucleotide polymorphism (SNP) variants in a Finnish sample of 1,151 type 2 diabetic patients and 953 control subjects. We confirmed the association with the same risk allele (*P* value <0.05) for all five SNPs. Our strongest results were for rs12255372 (odds ratio [OR] 1.36 [95% CI 1.15–1.61], *P* = 0.00026) and rs7903146 (1.33 [1.14–1.56], *P* = 0.00042). Based on the CEU HapMap data, we selected and tested 12 additional SNPs to tag SNPs in linkage disequilibrium with rs12255372. None of these SNPs showed stronger evidence of association than rs12255372 or rs7903146 (OR ≤1.26, *P* ≥ 0.0054). Our results strengthen the evidence that one or more variants in *TCF7L2* are associated with increased risk of type 2 diabetes. *Diabetes* 55:2649–2653, 2006

Transcription factor 7-like 2 (*TCF7L2*) encodes a transcription factor that plays a role in the Wnt signaling pathway (1). A complex of TCF7L2, B-catenin, and other cofactors form a complex that is required for transcription of target genes (1). In a fine-scale association study of a 10.5-Mb type 2 diabetes linkage region on chromosome 10q, Grant et al. (2) identified a microsatellite marker, DG10S478, in intron 3 of *TCF7L2* that was strongly associated with type 2 diabetes in an Icelandic sample of 1,185 case and 931 control subjects. The most strongly associated allele of DG10S478 was protective; the combination of all other alleles had an odds ratio (OR) of 1.50 (95% CI 1.31–1.71; $P = 2.1 \times 10^{-9}$). This result remained significant after correcting for all the alleles of the 228 microsatellite markers tested in the 10.5-Mb region. DG10S478 also was significantly associated with type 2 diabetes in samples of 228 case and 539 control subjects from Denmark, 361 case and 530 control subjects from the U.S., and in the combined Icelandic, Danish, and American (U.S.) samples (1.56 [1.42–1.73], $P = 4.7 \times 10^{-18}$) (2). Five nearby single nucleotide polymorphisms (SNPs) also showed strong evidence of type 2 diabetes association in these three case-control sample groups (2). These SNPs were in moderate to strong linkage disequilibrium (LD) (r^2 = 0.43–0.95) with the most strongly associated DG10S478 allele and, therefore, also with the combined risk allele (2). We genotyped these 5 SNPs and 12 additional SNPs in Finnish case-control samples and found evidence to support the association of *TCF7L2* with risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

We studied Finnish type 2 diabetic case subjects and normal glucose tolerant control subjects from the Finland-United States Investigation of NIDDM Genetics (FUSION) study (3,4) and from the Finrisk 2002 study, a population-based national risk factor survey in Finland (5). Diabetes was defined according to 1999 World Health Organization criteria (6) of fasting plasma glucose concentration ≥7.0 mmol/l or 2-h plasma glucose concentration ≥11.1 mmol/l, by report of diabetes medication use, or based on medical record review. Normal glucose tolerance (NGT) was defined as having fasting glucose <6.1 mmol/l and 2-h glucose <7.8 mmol/l. We selected 784 unrelated type 2 diabetic case subjects from the FUSION type 2 diabetes affected sibling pair families. We selected control subjects with NGT for the FUSION case subjects from three sources: 140 spouses of FUSION type 2 diabetic individuals, 217 subjects who had NGT by oral glucose tolerance tests at age 65 and 70 years, and 241 individuals from the Finrisk 2002 study sample. From the Finrisk 2002 study sample, we selected an additional set of 367 unrelated type 2 diabetic case subjects and 355 unrelated control subjects with NGT, approximately frequency matched for age, sex, and province of birth. Study protocols for the FUSION and Finrisk 2002 studies were approved by local ethics committees and/or institutional review boards of each participating recruitment or analysis site, and informed consent was obtained from all study participants.

SNP selection and genotyping. We genotyped the 5 *TCF7L2* SNPs described by Grant et al. (2) and 12 SNPs that tagged all 63 SNPs in LD of $r^2 > 0.2$ or $D' > 0.9$ with rs12255372 based on the CEPH (Utah residents with ancestry from northern and western Europe) samples from CEU HapMap (October 2005 release). We genotyped the 17 *TCF7L2* SNPs using the

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FUSION, Finland-United States Investigation of NIDDM Genetics; GIST, Genotype-IBD Sharing Test; LD, linkage disequilibrium; NGT, normal glucose tolerance; SNP, single nucleotide polymorphism.

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TABLE 1
Characteristics of the FUSION and Finrisk 2002 case and control samples

	FUSION cases and FUSION/Finrisk control subjects			Finrisk	
	FUSION case subjects	FUSION control subjects	Finrisk control subjects	Case subjects	Control subjects
n	784	357*	241	367	355
Male	435	144	168	219	207
Female	349	213	73	148	148
Age at diagnosis (years)	51.0 (12.0)	NA	NA	59.0 (12.0)	NA
Age at examination (years)	64.3 (10.1)	69.8 (5.7)	65.0 (10.0)	61.0 (12.0)	61.0 (11.0)
BMI (kg/m^2)	29.4 (6.1)	26.9 (5.3)	26.8 (4.3)	30.7 (6.4)	26.7 (4.5)
Fasting glucose (mmol/l)	9.7 (4.8)	5.0 (0.6)	5.6 (0.5)	7.2 (1.4)	5.6 (0.5)
Fasting insulin (pmol/l)	96.0 (84.0)	60.0 (36.0)	42.0 (28.8)	79.8 (61.2)	39.0 (28.8)

Data are median (interquartile range). *Two hundred seventeen FUSION elderly control subjects and 140 spouse control subjects. NA, not applicable.

Sequenom homogeneous MassEXTEND assay. We achieved an average genotype call rate of 97.0% and call rates ≥95.6% for each SNP. Our genotyping was 99.72% consistent based on six inconsistencies among 2,148 duplicate genotype pairs. Genotype data for all 17 SNPs were consistent with Hardy-Weinberg equilibrium in case subjects, in control subjects, and in combined case and control subjects ($P > 0.01$). All samples were also genotyped for *PPARG* P12A and *KCNJ11* E23K as described by Douglas et al. (7) or Willer et al. (personal communication).

Statistical analysis. Those individuals ($n = 34$) who were missing birthplace information were excluded from all analysis except LD estimation and Genotype-IBD Sharing Test (GIST; see below). We tested for type 2 diabetes–SNP association using logistic regression under the additive genetic model that is multiplicative on the OR scale, a dominant model, and a recessive model, with adjustment for 5-year age category, sex, and birth province. Within the additive model framework for each SNP with association *P* value <0.05, we tested the ability of any other genotyped SNP to significantly improve the model fit by comparing the fit of a model for the associated SNP to a model containing the associated SNP and one other SNP using a likelihood ratio test (8). To assess the joint risk conferred by the presence of risk alleles from three type 2 diabetes–associated genes, *PPARG* (P12A), *KCNJ11* (E23K), and *TCF7L2* (rs12255372), we counted the number of risk alleles for each individual and used the number of risk alleles to predict case/control status using logistic regression. We also directly calculated the OR for each number of risk alleles relative to three risk alleles.

We estimated pairwise LD measures using LDmax (9) and performed haplotype analysis using FAMHAP (10). We used a χ^2 test of homogeneity to compare allele frequencies among selected groups. We tested for heterogeneity of ORs using a χ^2 goodness-of-fit test (11).

In the FUSION case subjects, we assessed evidence for association between possession of the risk alleles and evidence of linkage in FUSION type 2 diabetes sibships (12) using the GIST (13).

RESULTS

We genotyped the five SNPs originally reported to be associated with type 2 diabetes by Grant et al. (2) in a Finnish sample of 1,151 type 2 diabetic case subjects and 953 control subjects with NGT from the FUSION (3,4) and Finrisk 2002 (5) studies (Table 1). We found significant evidence for type 2 diabetes association for all five of these SNPs ($P < 0.05$) with the same risk allele as the original report (2) (Table 2 and online appendix Table 1 [available at http://diabetes.diabetesjournals.org]). Our strongest evidence for type 2 diabetes association was for rs12255372, located in intron 4 (OR 1.36 [95% CI 1.15–1.61], $P = 0.00026$), and rs7903146, located in intron 3 (1.33 [1.14–1.56], $P = 0.00042$). These two SNPs are separated by 50 kb and were in moderately strong LD in our Finnish control subjects ($r^2 = 0.70$, $D' = 0.91$) (online appendix Table 2). Our strongest evidence for association was for an additive model (online appendix Table 1), which was consistent with the findings of Grant et al. (2). We combined three separate controls groups, two from FUSION and one from Finrisk, for comparison to the FUSION case subjects. We tested for heterogeneity of allele frequencies among these three control groups and found no significant differences (data not shown). The SNP–type 2 diabetes association OR estimates between the Finrisk and FUSION samples did not differ more frequently than expected by chance given the number of tests performed (online appendix Table 3).

To further investigate the type 2 diabetes *TCF7L2* association in this region, we genotyped 12 additional *TCF7L2* SNPs that tagged all 63 SNPs in LD of $r^2 > 0.2$ or $D' > 0.9$ with rs12255372 based on the CEU HapMap sample; these 12 SNPs all were within introns 3 (88 kb in length) and 4 (101 kb in length). Using this tag SNP set, we observed a region of high LD based on D′ that extended ~56 kb from the middle of intron 3 (rs17747324) to the first part of intron 4 (rs12255372) and contained the two most strongly associated SNPs, rs7903146 and rs12255372 (online appendix Table 2). In our sample, all but 2 of the 12 additional SNPs were in lower r^2 with rs12255372 than the other 4 SNPs from Grant et al. (2), and the 3 most distal SNPs were in lower LD with rs12255372 than predicted by the CEU HapMap sample (online appendix Table 2). Under an additive model, each of the 12 additional SNPs was less strongly associated with type 2 diabetes (OR ≤1.26, $P \geq 0.0054$) than rs12255372 or rs7903146 (Table 2).

Haplotype analysis did not reveal a risk haplotype that explained the association substantially more than any individual SNP. Within a logistic regression model framework, either of the two most strongly associated SNPs was, in our sample, sufficient to explain the observed association, since adding a second SNP did not significantly improve model fit.

Risk allele frequencies for the two SNPs with strongest type 2 diabetes associations, rs12255372 and rs7903146, were 8–12% (10–19%) lower in our Finnish control subjects (cases) than in the Icelandic, Danish, and American (U.S.) control subjects (cases) (Table 3). Allele frequencies for these SNPs did not vary significantly among the 13 historical Finnish provinces in control subjects ($P \geq 0.23$, data not shown).

In a linkage genome scan of 737 FUSION type 2 diabetic families, we observed modest evidence for type 2 diabetes linkage on chromosome 10q (logarithm of odds = 0.61) at 131.5 cM on the FUSION linkage map near microsatellite marker D10S1237, ~1 Mb distal to *TCF7L2* (12). Using GIST, we found evidence for an association between the presence of the risk allele in the FUSION type 2 diabetic case subjects and increased allele sharing identity by

TABLE 2
Comparison of ORs for *TCF7L2* SNPs genotyped in Finnish and in Icelandic, Danish, and American (U.S.) samples

SNP	*TCF7L2* location‡	Genomic position§	Relative position‖	Risk allele	Finnish sample (current study) OR¶	95% CI	Two-sided *P* value	Combined Icelandic, Danish, and American (U.S.) samples* OR¶	95% CI	Two-sided *P* value	Test for heterogeneity of OR between four samples† *P* value
rs11196175	Intron3	114726604	−72.288	C	1.16	0.59–1.35	0.070				
rs7079711	Intron3	114735778	−63.114	G	1.08	0.93–1.26	0.30				
rs11196181	Intron3	114739008	−59.884	G	1.01	0.81–1.26	0.94				
rs17747324	Intron3	114742493	−56.399	C	1.26	1.07–1.48	0.0054				
rs7901695	Intron3	114744078	−54.814	C	1.25	1.07–1.45	0.0042	1.49	1.35–1.65	3.9×10^{-15}	0.21
rs7903146	Intron3	114748339	−50.553	T	1.33	1.14–1.56	0.00042	1.54	1.39–1.70	2.1×10^{-17}	0.29
rs7896811	Intron3	114756707	−42.185	C	1.01	0.86–1.18	0.93				
rs11196192	Intron3	114772277	−26.615	G	1.35	0.97–1.87	0.080				
rs11196199	Intron3	114786107	−12.785	A	1.04	0.89–1.21	0.65				
rs17685538	Intron3	114787461	−11.431	C	1.14	0.96–1.36	0.14				
rs7895340	Intron4	114791515	−7.377	A	1.16	1.02–1.32	0.029	1.31	1.19–1.44	1.4×10^{-8}	0.45
rs11196205	Intron4	114797037	−1.855	C	1.15	1.01–1.31	0.030	1.31	1.19–1.44	4.6×10^{-8}	0.41
rs12255372	Intron4	114798892	0	T	1.36	1.15–1.61	0.00026	1.52	1.38–1.68	2.5×10^{-16}	0.41
rs11196213	Intron4	114811544	12.652	T	1.14	1.00–1.29	0.049				
rs11196228	Intron4	114854287	55.395	T	1.39	1.07–1.81	0.015				
rs290494	Intron4	114875861	76.969	G	1.14	0.94–1.37	0.18				
rs1555485	Intron4	114902524	103.632	C	1.02	0.88–1.18	0.82				

*From Grant et al. (2); see online appendix Table 4. †Test for OR heterogeneity between the individual Finnish, Icelandic, Danish, and American (U.S.) samples. ‡Intronic location from Ensemble ENST00000347863. §Genomic position on chromosome 10 in NCBI Build 35. ‖Genomic position (in kilobytes) relative to rs12255372. ¶OR calculated using an additive genetic model that in logistic regression is multiplicative on the OR scale.

descent within FUSION type 2 diabetes sibships for the four most strongly associated SNPs by case/control analysis, rs7903146, rs7901695, rs17747224, and rs12255372 ($P = 0.036$, 0.033, 0.055, and 0.064, respectively), suggesting that any of these SNPs may partially explain the observed linkage signal.

One of the underlying goals of type 2 diabetes genetic research is to identify individuals at higher or lower risk for disease based on the presence or absence of risk variants from multiple genes. Of SNPs that have been tested for type 2 diabetes association by multiple groups, *PPARG* P12A and *KCNJ11* E23K have been shown to be associated with type 2 diabetes in multiple studies (14–17) including FUSION (7) (Willer et al., personal communication). We examined the combined risk of type 2 diabetes from variants in *PPARG*, *KCNJ11*, and *TCF7L2* in our Finnish sample. Within our sample, the ORs from additive models for *PPARG* P12A (1.27 [95% CI 1.07–1.50]), *KCNJ11* E23K (1.23 [1.08–1.40]), and the *TCF7L2* rs12255372 allele T (1.35 [1.16–1.38]) did not differ significantly, and thus, we analyzed the data in terms of the total number of risk alleles for these three SNPs (0–6 risk alleles). Each risk allele increased the odds of type 2 diabetes, which approximates the increase in risk, by a factor of 1.26 (95% CI 1.15–1.38). For example, compared with individuals with the median number of three risk

TABLE 3
Comparison of allele frequencies for *TCF7L2* in Finnish, Icelandic, Danish, and American (U.S.) samples

SNP	Relative position*	Risk allele	Case/control status	Risk allele frequency Finnish	Icelandic†	Danish†	U.S.†	*P* value for testing of heterogeneity of allele frequencies With Finns	Without Finns
rs7901695	−54.814	C	Control	0.22	0.30	0.28	0.30	1.2×10^{-8}	0.48
			Case	0.25	0.39	0.35	0.40	$<1.0 \times 10^{-10}$	0.15
rs7903146	−50.553	T	Control	0.18	0.30	0.27	0.28	$<1.0 \times 10^{-10}$	0.27
			Case	0.22	0.39	0.36	0.40	$<1.0 \times 10^{-10}$	0.21
rs7895340	−7.377	A	Control	0.43	0.46	0.43	0.47	0.06	0.35
			Case	0.45	0.52	0.52	0.53	1.9×10^{-6}	0.90
rs11196205	−1.855	C	Control	0.43	0.47	0.44	0.48	0.015	0.13
			Case	0.45	0.53	0.52	0.54	1.8×10^{-7}	0.38
rs12255372	0	T	Control	0.16	0.28	0.26	0.26	$<1.0 \times 10^{-10}$	0.17
			Case	0.20	0.36	0.33	0.39	$<1.0 \times 10^{-10}$	0.12

*Genomic position (in kilobytes) relative to rs12255372 (114,798,892 on chromosome 10 in NCBI Build 35). †From Grant et al. (2); see online appendix Table 3.

TABLE 4
Effect of number of risk alleles from *PPARG*, *KCNJ11*, and *TCF7L2* on the odds of type 2 diabetes: comparison to the three risk allele category

Number of risk alleles	Proportion of Finnish sample	Assuming equal increase in OR for each additional risk allele*	Allowing for unequal increase in OR for each additional risk allele†		
		OR	OR	95% CI	*P* value
0	0.005	0.50	0.46	0.10–2.00	0.30
1	0.05	0.63	0.69	0.46–1.02	0.06
2	0.25	0.80	0.84	0.66–1.06	0.13
3	0.38	1.00	1.00	Ref.	
4	0.24	1.26	1.30	1.02–1.66	0.03
5	0.06	1.59	1.70	1.13–2.56	0.01
6	0.01	2.00	2.90	0.78–10.8	0.11

*Based on a 1.26-fold increase in OR for each additional risk allele (determined from an additive model for the number of risk alleles). †Independent estimation of the OR for each risk allele count.

alleles, individuals with one risk allele have 0.63-fold–higher risk of type 2 diabetes, and individuals with five risk alleles have 1.59-fold–higher risk of type 2 diabetes (Table 4). When we do not assume equal allele effects but instead calculate the OR for each number of risk alleles compared with the reference count of three risk alleles, we obtain similar OR estimates (Table 4).

DISCUSSION

We found type 2 diabetes association in Finns with the five type 2 diabetes–associated *TCF7L2* SNPs identified by Grant et al. (2). Our two most strongly associated SNPs had the strongest evidence of association in the combined Icelandic, Danish, and American (U.S.) samples. The ORs based on our Finnish sample were consistently lower than those reported by Grant et al. (2), but there was no evidence of heterogeneity in the ORs between our Finnish sample and the original Icelandic, Danish, and American (U.S.) samples for any of the five SNPs ($P = 0.21-0.45$) (Table 2).

We assayed 12 additional *TCF7L2* SNPs chosen to tag all known SNPs in LD with rs12255372 and did not find evidence of a more strongly associated variant. However, we have not assayed SNPs that cover the remainder of the gene, and other *TCF7L2* variants that increase of risk of type 2 diabetes may exist.

The risk allele frequencies for our two most strongly associated SNPs were substantially lower in Finnish case and control subjects than in the Icelandic, Danish, or American (U.S.) case and control subjects of Grant et al. (2), suggesting that there are underlying differences in the population allele frequencies rather than differences due to case or control sampling criteria.

We found evidence from GIST (13) that the associated variants partially explain the excess allele sharing identity by descent in the region of our modest linkage signal (logarithm of odds = 0.61) (12) on chromosome 10q, again suggesting that a variant or variants that increase the risk of type 2 diabetes are present in this region. However, in the Icelandic sample, these SNPs did not explain the observed linkage signal (2).

We found additive effects on the risk of type 2 diabetes for each additional risk allele from *TCF7L2*, *PPARG* (P12A), and *KCNJ11* (E23K). Hansen et al. (18) observed additive effects for the number of risk alleles from *PPARG* (P12A) and *KCNJ11* (E23K), and Hattersley et al. (19) observed additive effects for these alleles in combination with alleles from additional risk loci. These SNPs likely represent only a small proportion of the total set of genetic variants associated with the risk of type 2 diabetes; thus, an individual with multiple risk alleles from this particular set of three variants could still have a low risk of type 2 diabetes compared with others in the population. These OR estimates also may be biased relative to those that would be observed in the general population because a large proportion of our case subjects are from type 2 diabetes affected sibpair families and because we have excluded individuals with impaired glucose tolerance or impaired fasting glucose from our control group.

We tested the *TCF7L2* SNPs for quantitative trait association, including weight-related traits, blood pressure, fasting levels of insulin, glucose, lipids, and free fatty acids in FUSION case subjects; 2-h oral glucose tolerance test in FUSION control subjects; insulin and glucose in control subjects; and glucose effectiveness, acute insulin response, and insulin sensitivity and disposition index in spouse control subjects (3,4). We found no significant SNP trait associations after taking into account the number of tests. The most significant result was observed in the FUSION spouse group with lower disposition index in individuals with the G (putative risk) allele of rs11196192 ($P = 0.0020$) (data not shown).

In summary, we have confirmed the association of variants in *TCF7L2* with type 2 diabetes observed in the Icelandic, Danish, and American (U.S.) samples of Grant et al. (2). *TCF7L2* joins a growing list of transcription factors that are involved in the growth, development, and metabolism of type 2 diabetes and contain genetic variants that increase the risk of type 2 diabetes.

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