Impact of Common Variants of *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A*, *IGF2BP2*, and *CDKAL1* on the Risk of Type 2 Diabetes in 5,164 Indians

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OBJECTIVE—Common variants in *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A*, *IGF2BP2*, and *CDKAL1* genes have been shown to be associated with type 2 diabetes in European populations by genome-wide association studies. We have studied the association of common variants in these eight genes with type 2 diabetes and related traits in Indians by combining the data from two independent case–control studies.

RESEARCH DESIGN AND METHODS—We genotyped eight single nucleotide polymorphisms (*PPARG*-rs1801282, *KCNJ11*-rs5219, *TCF7L2*-rs7903146, *SLC30A8*-rs13266634, *HHEX*-rs1111875, *CDKN2A*-rs10811661, *IGF2BP2*-rs4402960, and *CDKAL1*-rs10946398) in 5,164 unrelated Indians of Indo-European ethnicity, including 2,486 type 2 diabetic patients and 2,678 ethnically matched control subjects.

RESULTS—We confirmed the association of all eight loci with type 2 diabetes with odds ratio (OR) ranging from 1.18 to 1.89 ($P = 1.6 \times 10^{-3}$ to 4.6×10^{-34}). The strongest association with the highest effect size was observed for *TCF7L2* (OR 1.89 [95% CI 1.71–2.09], $P = 4.6 \times 10^{-34}$). We also found significant association of *PPARG* and *TCF7L2* with homeostasis model assessment of β-cell function ($P = 6.9 \times 10^{-8}$ and 3×10^{-4}, respectively), which looked consistent with recessive and under-dominant models, respectively.

CONCLUSIONS—Our study replicates the association of well-established common variants with type 2 diabetes in Indians and shows larger effect size for most of them than those reported in Europeans. ***Diabetes*** **59:2068–2074, 2010**

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Type 2 diabetes is a complex metabolic disorder with both genetic and environmental factors such as food habits and lifestyle contributing to its pathogenesis (1). Due to its complex etiology, the progress of discovery of genetic components for type 2 diabetes had been very slow until the advent of high throughput genome-wide association (GWA) studies (2). Until recently, only a few common variants in *PPARG* (3), *KCNJ11* (4), and *TCF7L2* (5) were shown to be associated with type 2 diabetes. With the advent of GWA studies, there are at least 20 loci identified today that are associated with the risk of type 2 diabetes (6). The first GWA study in the French population revealed *SLC30A8* and *HHEX* as new loci for type 2 diabetes in addition to replicating the strong association with *TCF7L2* (7). Further, GWA studies added several new genes including *CDKAL1*, *CDKN2A*, *IGF2BP2*, and *FTO* to the list of type 2 diabetes–associated loci and confirmed the associations for *PPARG*, *KCNJ11*, and *TCF7L2* (8–12).

India harbors the maximum number of diabetic patients, which is projected to double by the year 2030 (13). Indians are diagnosed with diabetes a decade earlier and at a lower BMI than Europeans, which may be partly explained by their excess central obesity (14,15). Hence, determination of genetic risk factors predicting the risk of type 2 diabetes in the Indian population is highly desirable. Recent evidence suggests that the genetic basis of several diseases in Indians might be different from that of Europeans (16,17), which could be due to differences in the risk allele frequency and pattern of linkage disequilibrium. A report from the Indian Genome Variation Consortium also suggested that most of the populations in the Indian subcontinent are distinct from HapMap populations (18). Hence, genes associated with a disease in other populations need to be assessed for their role in the Indian population. The present study evaluated the association of eight most replicated and well-established genetic variants of *PPARG*, *KCNJ11*, *TCF7L2*, *SLC30A8*, *HHEX*, *CDKN2A*, *IGF2BP2*, and *CDKAL1* with type 2 diabetes and related quantitative traits in Indians. We also performed allele dosage analysis of these variants and investigated their influence on quantitative metabolic traits related to type 2 diabetes.

RESEARCH DESIGN AND METHODS

The study involved the participation of 5,164 individuals comprising 2,486 patients with type 2 diabetes of Indo-European ethnicity and 2,678 ethnically

TABLE 1
Basic anthropometric and clinical characteristics of the study groups from two centers

Characteristics	Delhi		Pune	
	Type 2 diabetic patients	Control subjects	Type 2 diabetic patients	Control subjects
n (men/women)	1,019 (592/427)	1,006 (606/400)	1,467 (826/641)	1,672 (884/788)
Age (years)	53 (45–62)	50 (44–60)	46 (40–52)	33 (29–37)
Age of diagnosis (years)	45 (39–52)	—	38.5 (33.3–42.2)	—
Individuals on medication for lipids (%)	4.00	—	22.70	—
BMI (kg/m^2)				
Women	26.70 (24.20–29.20)	24.90 (21.10–28.60)	26.90 (24.40–29.60)	19.53 (17.60–22.74)
Men	23.80 (22.00–26.00)	23.20 (20.20–25.70)	24.90 (22.80–27.70)	21.18 (19.15–23.62)
Waist-to-hip ratio				
Women	1.00 (0.97–1.03)	0.86 (0.82–0.92)	0.89 (0.85–0.94)	0.76 (0.73–0.80)
Men	1.00 (0.97–1.03)	0.97 (0.92–1.00)	0.97 (0.94–1.02)	0.91 (0.86–0.95)
FPG (mmol/l)	7.90 (6.40–10.30)	4.90 (4.50–5.30)	8.50 (6.90–11.30)	5.11 (4.67–5.56)
2-h PPG (mmol/l)	—	5.60 (5.80–6.30)	—	5.50 (4.56–6.50)
Total cholesterol (mmol/l)	4.20 (3.50–5.00)	4.40 (3.70–5.10)	4.10 (3.50–4.80)	3.77 (3.28–4.33)
Triglycerides (mmol/l)	1.60 (1.10–2.20)	1.30 (1.00–1.80)	1.40 (1.00–1.20)	0.84 (0.62–1.20)
HDL cholesterol (mmol/l)	1.03 (0.88–1.22)	1.06 (0.88–1.28)	1.03 (0.90–1.18)	1.03 (0.87–1.23)
FPI (pmol/l)	—	32.20 (17.50–57.20)	—	32.50 (20.84–49.18)
HOMA-IR	—	1.16 (0.59–2.02)	—	1.21 (0.76–1.89)
HOMA-B	—	73.40 (40.70–138.60)	—	69.73 (44.39–109.79)

Data are median (interquartile range).

matched control subjects recruited from two places—Delhi in northern India and Pune in western India. Subjects in the Delhi study (comprised of 1,019 patients and 1,006 control subjects) were enrolled on the basis of inclusion and exclusion criteria as described earlier (19). The consecutive subjects diagnosed as type 2 diabetic patients according to World Health Organization criteria (20) at the Endocrinology Clinic of the All India Institute of Medical Sciences were included in the study. The inclusion criteria for control subjects were ≥40 years of age, A1C ≤6.0%, fasting glucose ≤6.11 mmol/l, no history of diabetes in first- or second-degree relatives, and urban dweller of Indo-European ethnicity.

From Pune, 1,467 type 2 diabetic patients and 1,672 control subjects of Indo-European ethnicity were recruited for the study. Type 2 diabetic patients were diagnosed before 45 years of age according to World Health Organization criteria (20). The control group consisted of ethnically matched individuals recruited from different population cohorts including the Pune Maternal Nutrition Study, the Pune Children's Study, and the Coronary Risk of Insulin Sensitivity in Indian Subjects study (21).

Subjects with ketoacidosis at diagnosis, clinically judged to be insulin dependent, with exocrine pancreatic disease (fibrocalculous pancreatic diabetes), and who fulfilled the clinical criteria of maturity-onset diabetes of the young were excluded from the study. Pregnant women were also excluded from the study. Informed consent was obtained from all the participants and the study was approved by the ethics committees of the participating institutions in accordance with the principles of the Helsinki Declaration.

Clinical measurements. All the subjects in both studies were extensively characterized for different anthropometric and quantitative metabolic traits. Anthropometric measurements, including height, weight, and waist and hip circumferences, were done per standardized protocols, and BMI and waist-to-hip ratio were calculated. Biochemical measurements including levels of A1C, fasting plasma glucose (FPG), 2-h postprandial glucose (PPG), fasting plasma insulin (FPI), total cholesterol, HDL cholesterol, and triglycerides were performed using standard laboratory assays as described earlier (19,22). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the formula: (FPI in mU/ml × FPG in mmol/l)/22.5 and homeostasis model assessment of β-cell function (HOMA-B) was calculated using the equation: (FPI in mU/ml × 20)/(FPG in mmol/l − 3.5) as reported previously (23).

Genotyping. Eight well-replicated single nucleotide polymorphisms (SNPs) from eight genes identified through GWA studies were selected for association with type 2 diabetes. These included SNPs-rs1801282 (*PPARG*), rs5219 (*KCNJ11*), rs7903146 (*TCF7L2*), rs13266634 (*SLC30A8*), rs1111875 (*HHEX*), rs10811661 (*CDKN2A*), rs4402960 (*IGF2BP2*), and rs10946398 (*CDKAL1*). In the samples from Delhi, these eight SNPs were genotyped using Illumina Golden Gate assay as a part of 1,536-plex assay and following the manufacturer's instructions (http://www.illumina.com/downloads/GOLDENGATEASSAY.pdf). Quality control criteria for the SNPs to qualify for further analysis included: genotype confidence score of >0.25, call frequency >0.9, GenTrans score >0.6, cluster separation score >0.4, minor allele frequency >0.05, and Hardy-Weinberg equilibrium (HWE) in control subjects ($P > 0.0031$). A total of 147 samples (7.2%) were genotyped in duplicate, and an error rate of <0.01 was estimated. Further, to validate the genotype calls, 10% of the SNPs were re-genotyped for 180 samples using Sequenom-based MassARRAY technology, and a concordance rate of >99.7% was observed.

The genotyping of all the SNPs in the subjects from Pune was performed using Sequenom-based MassARRAY technology. Genotypes for ~10% of the samples were confirmed by sequencing on an ABI 3730 Genetic Analyzer using specific primers, and inconsistency of only 0.06% (2/3,452) was observed.

Statistical analysis. We examined the association of the above-mentioned SNPs in eight genes with type 2 diabetes and related traits in the Delhi and Pune studies separately and also after combining the samples from both of the studies. The distributions of genotype for all the SNPs were analyzed for deviation from HWE using χ^2 analysis. Cochran Q-statistics was performed to assess heterogeneity between the two groups. Logistic regression analysis assuming log additive model was performed to determine the association between SNPs and the risk for type 2 diabetes. The associations were adjusted for sex, age, BMI, and geographical region, as appropriate. The odds ratios (ORs) with 95% CIs were presented with respect to the risk allele as observed in the initial studies on Europeans (9). A P value of < 0.0062 ($\alpha = 0.05/8$) was considered significant for association with type 2 diabetes in the combined samples after correcting for multiple testing. The association of each SNP with continuous traits was performed by pooling the data of control subjects from both of the studies using the Kruskal-Wallis test. Initially a priori power was calculated based on the risk allele frequency (RAF) and effect sizes reported in the Europeans. Subsequently, posterior power calculation was performed based on the RAF and effect sizes from our study, assuming log additive model using Quanto software (http://hydra.usc.edu/gxe/) at $\alpha = 0.05$ and $\alpha = 0.0062$ (corrected P value), and assuming 10% prevalence of type 2 diabetes. For rs7903146 (*TCF7L2*), we combined the published data of the Pune study (22) with that of the Delhi study data.

The combined effect of the eight SNPs on the risk of type 2 diabetes was determined through allele dosage analysis by categorizing the subjects based on the number of "effective" risk alleles. The analysis included only those individuals in whom genotypes at all eight SNPs were available. Since the effect sizes (defined by the SNP-specific ORs) were not uniform, the allele dosage score of an individual was computed by the weighted mean of the proportion of risk alleles at the eight SNPs (i.e., one for two risk alleles, 0.5 for one risk allele, and 0 for no risk allele) with weights as the relative log ORs of different SNPs. The "effective" number of risk alleles was obtained as the allele dosage score multiplied by 16 (maximum number of risk alleles corresponding to eight SNPs). Considering subjects with six or fewer number of "effective"

TABLE 2
Association of SNPs with type 2 diabetes in the Delhi and Pune studies and the combined study

		Delhi				
		n Case/control subjects	RAF			
SNP (gene)	Risk/non-risk allele*		Case subjects	Control subjects	OR (95% CI)†	*P*
rs1801282 (*PPARG*)	C/G	1,019/1,004	0.89	0.86	1.30 (1.08–1.57)	0.006
rs5219 (*KCNJ11*)	T/C	1,017/1,006	0.39	0.35	1.17 (1.02–1.33)	0.02
rs7903146 (*TCF7L2*)	T/C	1,017/1,006	0.40	0.29	1.67 (1.46–1.92)	1.7×10^{-13}
rs13266634 (*SLC30A8*)	C/T	1,010/1,000	0.79	0.75	1.32 (1.13–1.53)	0.0003
rs1111875 (*HHEX*)	G/A	1,018/1,003	0.47	0.42	1.29 (1.13–1.47)	0.0001
rs10811661 (*CDKN2A*)	T/C	1,019/1,006	0.89	0.87	1.3 (1.07–1.59)	0.009
rs4402960 (*IGF2BP2*)	T/G	1,019/1,006	0.46	0.42	1.18 (1.03–1.33)	0.02
rs10946398 (*CDKAL1*)	C/A	1,006/990	0.24	0.21	1.19 (1.03–1.38)	0.02

*Risk alleles as identified in earlier European studies (9). †Analysis adjusted for sex, age, and BMI. ‡Analysis adjusted for sex, age, BMI, and geographical region (Delhi and Pune). *n*, number of subjects genotyped; OR, odds ratio per allele; RAF, risk allele frequency.

risk alleles as the reference group, ORs and *P* values for every unit increase in the number of "effective" risk alleles were calculated after adjusting for sex, age, BMI, and geographical region. All statistical analyses were performed using PLINK version 1.05 (http://pngu.mgh.harvard.edu/_purcell/plink) (24) and SPSS version 17.0 (SPSS, Chicago, IL) unless specified otherwise.

RESULTS

The clinical characteristics of the subjects in both of the studies are presented in Table 1. The genotype distributions at all the SNPs were in HWE ($P > 0.0031$ in control subjects).

In the Delhi study, the association analysis with type 2 diabetes revealed that all the eight SNPs were significantly associated with type 2 diabetes at $\alpha = 0.05$ and remained so after adjustment for sex, age, and BMI with ORs ranging from 1.17 to 1.67 and *P* values ranging from 0.02 to 1.7×10^{-13} (Table 2, and supplementary Table 1 in the online appendix, available at http://diabetes.diabetesjournals.org/cgi/content/full/db09-1386/DC1). Consistent with earlier findings, we also observed the strongest association at rs7903146 of *TCF7L2* with OR 1.67 (95% CI [1.46–1.92], $P = 1.7 \times 10^{-13}$).

In the Pune study, all the SNPs except for rs10946398 (*CDKAL1*) were significantly associated with type 2 diabetes and retained significance after adjusting for sex, age, and BMI (Table 2, supplementary Table 1). Similar to the observation in the Delhi study, the *TCF7L2* variant showed the strongest association with OR 2.10 (95% CI [1.77–2.49], $P = 1.7 \times 10^{-17}$).

There was no significant heterogeneity of ORs for any of the variants between the Delhi and Pune studies ($P > 0.05$ for Cochran Q-statistics), hence we performed association analysis by combining their genotype data. All the eight SNPs were significantly associated with type 2 diabetes and adjustment for covariates like age, sex, BMI, and geographical region did not nullify the significance (Table 2, supplementary Table 1). ORs for the associations in the combined analysis ranged from 1.18 to 1.89 with *P* values ranging from 1.6×10^{-3} to 4.6×10^{-34}. The RAF of three variants (rs5219, rs7902146, and rs10946398) differed significantly between the control subjects of the two studies (Table 2). Meta-analysis performed by combining the summary data of the two studies, both under the fixed- and random-effect models, also confirmed the association of these SNPs with type 2 diabetes, except for rs5219 under the random-effect model (supplementary Table 2). The estimated OR for rs5219 was higher under the random-effect model than the fixed effect model, which is known to yield more biased estimates. A priori power calculations showed that our study had >62% power at $\alpha = 0.05$ and >32% at $\alpha = 0.0062$ (supplementary Table 3) for detecting the association for the risk of type 2 diabetes for all SNPs. The effect sizes observed for all variants in our study populations were higher compared with that of Europeans (Table 3). However, the CI for two of them (*IGF2BP2* and *CDKAL1*) included the ORs observed in Europeans.

Allele dosage analysis revealed a significantly enhanced risk of type 2 diabetes by 1.31-fold with the increase in

TABLE 3
Comparison of effect sizes of the SNPs in Indians and Europeans

					Indians†		Europeans‡	
Gene	SNP	Risk/non-risk allele*	RAF in Indians	RAF in Europeans	OR (95% CI)	*P*	OR (95% CI)	*P*
PPARG	rs1801282	C/G	0.87	0.86	1.37 (1.19–1.59)	1.6×10^{-5}	1.14 (1.08–1.20)	1.7×10^{-6}
KCNJ11	rs5219	T/C	0.31	0.47	1.39 (1.26–1.54)	6.7×10^{-11}	1.14 (1.10–1.19)	6.7×10^{-11}
TCF7L2	rs7903146	T/C	0.24	0.26	1.89 (1.71–2.09)	4.6×10^{-34}	1.37 (1.31–1.43)	1.0×10^{-48}
SLC30A8	rs13266634	C/T	0.77	0.65	1.34 (1.20–1.50)	3.4×10^{-7}	1.12 (1.07–1.16)	5.3×10^{-8}
HHEX	rs1111875	G/A	0.43	0.53	1.27 (1.16–1.39)	5.7×10^{-7}	1.13 (1.09–1.17)	5.7×10^{-10}
CDKN2A	rs10811661	T/C	0.86	0.83	1.37 (1.18–1.59)	5.1×10^{-5}	1.20 (1.14–1.25)	7.8×10^{-25}
IGF2BP2	rs4402960	T/G	0.44	0.29	1.20 (1.09–1.33)	2.6×10^{-3}	1.14 (1.11–1.18)	8.9×10^{-36}
CDKAL1	rs10946398	C/A	0.24	0.31	1.18 (1.07–1.32)	1.6×10^{-3}	1.12 (1.08–1.16)	4.1×10^{-11}

*Risk alleles in Europeans, as indicated by DGI study (9). †ORs and *P* values obtained for combined analysis of data from the Delhi and Pune studies. ‡ORs and *P* values obtained from combined analysis of the Diabetes Genetics Initiative (DGI), Finland-United States Investigation of NIDDM Genetics (FUSION), and Wellcome Trust Case Control Consortium (WTCCC) studies (9). OR, odds ratio per allele; RAF, risk allele frequency.

TABLE 2
Continued

Pune						Combined				
n Case/control subjects	RAF		OR (95% CI)†	*P*	*P* (difference in allele frequencies)	*n* Case/control subjects	RAF		OR (95% CI)‡	*P*
	Case subjects	Control subjects					Case subjects	Control subjects		
1,422/1,553	0.91	0.87	1.47 (1.15–1.88)	1.8×10^{-3}	0.21	2,441/2,557	0.90	0.87	1.37 (1.19–1.59)	1.6×10^{-5}
1,417/1,397	0.40	0.28	1.84 (1.55–2.18)	4.4×10^{-12}	8.1×10^{-7}	2,434/2,403	0.40	0.31	1.39 (1.26–1.54)	6.7×10^{-11}
1,423/1,515	0.37	0.21	2.10 (1.77–2.49)	1.7×10^{-17}	4.5×10^{-9}	2,439/2,521	0.38	0.24	1.89 (1.71–2.09)	4.6×10^{-34}
1,456/1,539	0.81	0.78	1.25 (1.04–1.51)	0.02	0.03	2,466/2,539	0.80	0.77	1.34 (1.20–1.50)	3.4×10^{-7}
1,454/1,598	0.47	0.43	1.20 (1.03–1.39)	0.02	0.81	2,472/2,601	0.47	0.43	1.27 (1.16–1.39)	5.7×10^{-7}
1,431/1,086	0.89	0.86	1.43 (1.09–1.87)	0.01	0.90	2,450/2,092	0.89	0.86	1.37 (1.18–1.59)	5.1×10^{-5}
1,444/868	0.50	0.46	1.30 (1.08–1.56)	5.5×10^{-3}	0.03	2,463/1,874	0.48	0.44	1.20 (1.09–1.33)	2.6×10^{-3}
1,456/1,512	0.27	0.26	1.17 (0.98–1.38)	0.08	3.3×10^{-4}	2,462/2,501	0.26	0.24	1.18 (1.07–1.32)	1.6×10^{-3}

each unit of "effective" risk allele ($P = 2.7 \times 10^{-39}$) (Fig. 1). Individuals with 11 or more "effective" risk alleles (13.64%) carried 6.45-fold increased risk for type 2 diabetes in comparison with individuals having 6 or less "effective" risk alleles (7.89%) ($P = 7 \times 10^{-24}$).

We then examined the association of genetic variants with various quantitative traits in the control subjects from the two studies (Table 4, supplementary Table 5). We observed significant associations for *PPARG* and *TCF7L2* with HOMA-B ($P = 6.9 \times 10^{-8}$ and 3×10^{-4}, respectively). The association of *PPARG* looked consistent with a recessive model and that of *TCF7L2* looked consistent with an under-dominant model (heterozygotes have lower HOMA-B than either of the homozygotes as opposed to showing a continuous trend across the genotypes). We also found nominal association of *KCNJ11* with FPG ($P = 0.004$), HOMA-IR ($P = 0.04$), and waist-to-hip ratio ($P = 0.01$); *TCF7L2* with FPG ($P = 0.03$) and 2-h PPG ($P = 0.03$); and HHEX with FPI ($P = 0.04$) and HOMA-IR ($P = 0.02$). However, none of the associations for the quantitative trait analysis, except for *PPARG* and *TCF7L2* with HOMA-B, remained significant after correcting for multiple testing ($P_{\text{corrected}} = 0.000625$, 0.05/80).

DISCUSSION

Genome-wide association studies have resulted in the identification of a number of loci associated with type 2 diabetes—from just 3 confirmed loci in 2006 to 20 in 2009 (6). In the present study, we investigated the association of eight common and well-established common genetic variants with type 2 diabetes in 5,148 Indians. We combined the data from two independent studies of Indo-European individuals to increase the power of the study. To our knowledge, this is the largest study reported for the association of type 2 diabetes in Indians.

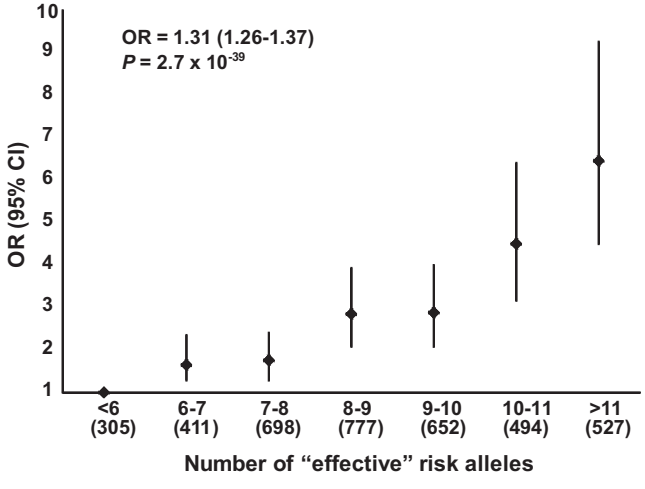

FIG. 1. Effect of increase in the number of "effective" risk alleles on the risk of type 2 diabetes in combined samples. OR and 95% CI are plotted on the *y*-axis for the corresponding number of "effective" risk alleles on the *x*-axis. Numbers in parentheses on *x*-axis indicate sample size in each category.

Among all the loci, *TCF7L2* so far has shown the strongest association with the largest effect size for type 2 diabetes in Europeans (5,7–12), Amish (25), and Indians (22,26,27), but not in Chinese (28) and Japanese (29) subjects. The present study confirms the association of *TCF7L2* with type 2 diabetes with the largest effect size. The *TCF7L2* gene product has been implicated in blood glucose homeostasis (5,30), and the variant rs7903146 is reported to be associated with measures of glucose metabolism (25). Consistent with these observations, we also found a strong association of *TCF7L2* with HOMA-B and a nominal association with FPG and 2-h PPG, confirming the physiological role of *TCF7L2* in glucose homeostasis.

Studies evaluating the association of the Pro12Ala variant of the *PPARG* gene with type 2 diabetes have reported contradictory results. The minor allele (Ala) at this locus has been shown to confer protection against type 2 diabetes by many studies (31–34) while in several other studies it has been found to predict susceptibility for type 2 diabetes (35,36). Moreover, association analysis of Pro12Ala in Asian Indians has also shown inconsistent findings (27,37) that might be attributed to the differences in the ethnicity of the subjects in these studies, or the studies may have been underpowered for detecting the direction of the association. We established the strong protective effect of the Ala allele against the development of type 2 diabetes in Indians.

Variant E23K (rs5219) in *KCNJ11* has been shown to be associated with type 2 diabetes in Europeans and Japanese (4,38) subjects, and our study replicates this significant association. The polymorphisms in *SLC30A8* and *HHEX* were identified by GWA studies in several European populations and subsequently was replicated in Asians (38–40). However, the association could not be validated in the Indian Sikh population, which was probably due to the small sample size and the low power of the study (27). With a larger sample size and higher power, we confirmed the strong association of *SLC30A8* and *HHEX* SNPs with type 2 diabetes in our combined data. The variant rs13266634 in *SLC30A8* has been shown to be

TABLE 4
Association of SNPs with quantitative traits (glucose and insulin metabolism) in combined control subjects

Gene SNP	Genotypesmajor hetero minor	n	FPG (mmol/l) Median (IQR)	P‡	2-h PPG (mmol/l) Median (IQR)	P‡	FPI (pmol/l) Median (IQR)	P‡	HOMA-IR Median (IQR)	P‡	HOMA-B Median (IQR)	P‡
PPARG	CC	1,932	5.03 (4.61–5.43)		5.50 (4.56–6.50)		32.99 (20.00–51.46)		1.21 (0.71–1.92)		72.58 (43.10–116.82)	
rs1801282	CG	578	5.03 (4.61–5.41)		5.61 (4.72–6.43)		30.42 (19.69–47.14)		1.13 (0.69–1.86)		67.19 (43.87–117.43)	
(C/G)	GG	47	4.94 (4.72–5.28)	0.39	5.50 (4.61–6.26)	0.49	27.80 (15.45–44.60)	0.13	1.02 (0.51–1.62)	0.33	65.36 (36.36–105.99)	6.9×10^{-8}*
KCNJ11	CC	1,143	5.00 (4.59–5.39)		5.50 (4.56–6.50)		32.00 (19.93–48.82)		1.18 (0.70–1.87)		71.68 (42.47–116.18)	
rs5219	CT	1,016	5.07 (4.71–5.44)		5.50 (4.57–6.44)		32.66 (20.02–51.81)		1.21 (0.73–1.94)		68.27 (44.32–112.37)	
(C/T)	TT	244	5.06 (4.64–5.46)	0.004*	5.44 (4.50–6.33)	0.63	32.33 (19.26–55.95)	0.70	1.22 (0.65–1.96)	0.04*	73.89 (39.33–122.34)	0.09
TCF7L2	CC	1,449	5.00 (4.61–5.44)		5.33 (4.50–6.28)		32.26 (19.23–49.64)		1.18 (0.69–1.87)		71.83 (42.75–115.76)	
rs7903146	CT	919	5.06 (4.61–5.44)		5.67 (4.70–6.56)		31.39 (20.04–52.00)		1.18 (0.71–1.96)		68.89 (42.29–118.40)	
(C/T)	TT	153	5.00 (4.66–5.38)	0.03*	5.64 (4.78–6.52)	0.03*	34.32 (19.32–53.74)	0.65	1.23 (0.72–1.87)	0.97	72.56 (41.30–111.24)	3×10^{-4}*
SLC30A8	CC	1,487	5.03 (4.64–5.44)		5.44 (4.56–6.44)		32.50 (19.80–50.00)		1.19 (0.71–1.89)		69.79 (43.88–115.71)	
rs13266634	CT	911	5.03 (4.61–5.39)		5.61 (4.78–6.44)		32.16 (19.86–51.00)		1.21 (0.69–1.90)		71.09 (41.60–118.98)	
(C/T)	TT	141	4.94 (4.50–5.34)	0.28	5.22 (4.34–6.47)	0.17	28.25 (18.17–45.16)	0.08	1.00 (0.63–1.79)	0.05	74.62 (42.25–114.14)	0.46
HHEX	AA	847	5.03 (4.61–5.39)		5.44 (4.56–6.44)		34.00 (20.00–53.86)		1.26 (0.72–2.02)		73.85 (45.07–119.81)	
rs1111875	AG	1,274	5.00 (4.61–5.44)		5.44 (4.56–6.51)		31.39 (20.34–48.18)		1.16 (0.72–1.81)		68.49 (43.03–114.09)	
(A/G)	GG	480	5.06 (4.64–5.46)	0.17	5.67 (4.67–6.39)	0.20	32.93 (18.99–54.00)	0.04*	1.25 (0.68–2.02)	0.02*	72.74 (41.51–120.19)	0.48
CDKN2A	TT	1,554	5.06 (4.67–5.44)		5.39 (4.50–6.39)		32.64 (19.74–51.12)		1.21 (0.69–1.94)		70.52 (42.57–114.69)	
rs10811661	TC	497	5.02 (4.57–5.44)		5.44 (4.56–6.41)		30.72 (19.14–53.85)		1.15 (0.68–1.96)		66.10 (40.97–115.21)	
(T/C)	CC	41	4.94 (4.73–5.61)	0.27	5.20 (4.35–6.26)	0.74	32.71 (21.74–59.87)	0.58	1.27 (0.77–2.03)	0.90	62.75 (40.79–103.38)	0.31
IGF2BP2	GG	591	5.00 (4.65–5.38)		5.36 (4.56–6.39)		33.02 (20.28–51.86)		1.24 (0.73–1.95)		74.87 (44.54–122.09)	
rs4402960	GT	919	5.03 (4.61–5.44)		5.39 (4.50–6.26)		30.54 (18.54–50.77)		1.13 (0.65–1.88)		65.27 (40.79–111.48)	
(G/T)	TT	364	5.06 (4.72–5.38)	0.69	5.50 (4.50–6.44)	0.64	31.43 (18.85–49.22)	0.23	1.15 (0.69–1.81)	0.31	67.48 (42.35–109.40)	0.18
CDKAL1	AA	1,466	5.05 (4.61–5.44)		5.52 (4.67–6.50)		32.16 (19.00–51.81)		1.17 (0.68–1.93)		68.88 (40.87–116.96)	
rs10946398	AC	875	5.06 (4.68–5.44)		5.56 (4.50–6.56)		32.50 (20.44–49.18)		1.23 (0.74–1.90)		72.10 (45.05–113.93)	
(A/C)	CC	160	5.08 (4.61–5.39)	0.78	5.00 (4.39–6.11)	0.14	34.40 (21.60–55.58)	0.05	1.28 (0.79–2.14)	0.06	78.54 (48.10–121.61)	0.05

Data are median (interquartile range). *Significant P value. ‡Analysis adjusted for sex, age, BMI, and geographical region. IQR, interquartile range.

associated with FPG and BMI (39,40), but we did not find any association with either of these parameters.

Variants of the *CDKAL1* gene have been linked to glucotoxicity (8) and have been shown to be associated with insulin secretion (8), A1C, and HOMA-B (41). We found significant association of the *CDKAL1* variant with type 2 diabetes but with none of the quantitative traits. We also found significant association for the variant rs10811661, which lies near the *CDKN2A* gene, with the risk of type 2 diabetes. This SNP was not associated with type 2 diabetes in a recent study of Indian Sikhs (27), stressing on the importance of adequate sample size with sufficient power. Consistent with previous studies, we also provided evidence for the association of rs4402960 in *IGF2BP2* with type 2 diabetes (27,38–40).

While all the eight loci independently predicted the risk for type 2 diabetes, this increased significantly if all the alleles were present together. A 1.31 times enhanced risk with the increase in each unit of "effective" risk allele and 6.45-fold risk among individuals carrying 11 or more "effective" risk alleles compared with individuals with 6 or less "effective" risk alleles underlines the additive influence of these genetic variants on risk for type 2 diabetes and their likely role in predictive genetic testing. Furthermore, several variants were found to have higher effect sizes in our study population in comparison with Europeans. This might be an indication of higher penetration of these variants for the risk of type 2 diabetes in Indians. However, the CIs for two of them (*IGF2BP2* and *CDKAL1*) include the OR estimated in the Europeans suggesting a similar effect size in both. It is worth mentioning that other six loci (*PPARG*, *TCF7L2*, *KCNJ11*, *SLC30A8*, *CDKN2A*, and *HHEX*), whose effect sizes are higher compared with those of Europeans, also show higher effect sizes when compared with East Asians (28,29,32–34, 38,39,40). Thus, the risk alleles at a few type 2 diabetes–associated loci have higher penetration in Indians compared with Europeans and East Asians subjects.

Population stratification is a major confounder for any association analysis. To address this issue, we have recruited case and control subjects from the same area for both the Delhi and Pune studies to minimize the chance for population stratification in the Indian context (18). However, given the diversity of Indian population, this possibility cannot be completely eliminated in the present study.

In conclusion, we replicated the association of eight major common variants of *PPARG*, *KCNJ11*, *TCF7L2*, *CDKAL1*, *HHEX*, *SLC30A8*, *CDKN2A*, and *IGF2BP2* with type 2 diabetes in Indians of Indo-European origin with an increased effect size compared with Europeans. Although our study is the largest and is an adequately powered study that has investigated the genetic basis of type 2 diabetes in Indians, a larger study of different ethnic groups including Dravidians will aid in better understanding their penetration, the likely effect of these genes on various quantitative traits, and the potential use as diagnostic markers for the susceptibility to type 2 diabetes in the diabetic capital of the world.

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