Introduction

Type 2 diabetes, a disease that is 4- to 6-fold more common in South Asian individuals than Europeans, is characterised by impaired glucose homeostasis resulting from a combination of beta cell dysfunction and insulin resistance. This inability to adequately regulate blood glucose levels is also linked to both micro- and macro-vascular complications. Recently, the Meta-Analysis of Glucose and Insulin related traits Consortium (MAGIC) identified 16 genetic variants robustly associated with fasting glucose in non-diabetic populations of European origin [1]. Although a number of these single nucleotide polymorphisms (SNPs) were also associated with type 2 diabetes, several were not, suggesting that some variants may be associated with a ‘physiological’ variation in glucose levels without influencing ‘pathological’ variation and type 2 diabetes risk [1]. As with other genetic associations, replication of these findings in datasets of different ethnic origin is an important step in helping to fine-map the aetiological variants at these loci. Our aim was to investigate the effect of these 16 SNPs on fasting glucose levels and type 2 diabetes in South Asian populations of Punjabi ancestry.
Genotyping

All subjects [UKADS, n = 1274; DGP, n = 1988; total, n = 3262] were genotyped for the 16 SNPs using the KASPar method (KBioscience, Hoddesdon, UK). Genotyping success rates were >96% for each SNP. Approximately 10% of samples were genotyped as blind duplicates resulting in an error rate of <1% for each SNP. Genotype counts in the two study populations are shown in Table 1.

Table 1. Demographic and health characteristics of study participants in the two populations.

| Demographic/Health | UKADS | DGP | UKADS/DGP |
|--------------------|-------|-----|-----------|
| Age (years)        | 54.9  | 56.9| 56.3      |
| Fasting plasma glucose (mmol/l) | 5.3   | 5.5 | 0.6       |
| Random blood glucose (mmol/l)    | 5.3 (0.9)| 5.5 (0.6)|          |
| HbA1c (%)           | 8.3   | 9.6 | 3.2       |
| BMI (kg/m²)         | 28.0  | 28.6| 24.3      |

All values except n are means (SD). T2D = type 2 diabetes. Within the UKADS control group BMI data were only available for 256 subjects.
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Table 2. Association of SNPs with type 2 diabetes in the UKADS and DGP study populations.

| Nearest gene | SNP | Allele (Risk/other) | RAF | OR (95% CI) | p    | RAF | OR (95% CI) | p    | RAF | OR (95% CI) | p    |
|--------------|-----|---------------------|-----|-------------|------|-----|-------------|------|-----|-------------|------|
| MTNR1B       | rs10830963 | G/C | 0.42 | 0.93 (0.79, 1.10) | 0.403 | 0.39 | 0.99 (0.88, 1.13) | 0.92 | 0.40 | 0.97 (0.88, 1.07) | 0.558 |
| ADRA2A       | rs10885122 | G/T | 0.79 | 0.94 (0.76, 1.15) | 0.525 | 0.75 | 1.13 (0.98, 1.32) | 0.10 | 0.76 | 1.06 (0.94, 1.20) | 0.339 |
| C2CD4B       | rs11371567 | A/G | 0.70 | 0.93 (0.77, 1.12) | 0.458 | 0.68 | 0.92 (0.80, 1.05) | 0.21 | 0.68 | 0.92 (0.83, 1.03) | 0.147 |
| SLC30A8      | rs11558471 | C/T | 0.71 | 0.93 (0.93, 1.54) | 0.242 | 0.74 | 1.14 (0.99, 1.33) | 0.07 | 0.73 | 1.13 (1.01, 1.27) | 0.034 |
| CRY2         | rs11605924 | A/C | 0.48 | 0.94 (0.82, 1.06) | 0.143 | 0.49 | 0.94 (0.82, 1.06) | 0.30 | 0.49 | 1.00 (0.91, 1.11) | 0.974 |
| ADCA5        | rs11708067 | A/G | 0.74 | 1.26 (1.04, 1.54) | 0.019 | 0.77 | 1.21 (1.03, 1.41) | 0.02 | 0.76 | 1.23 (1.09, 1.39) | 0.001 |
| SLC2A2       | rs11920090 | T/A | 0.85 | 0.94 (0.78, 1.12) | 0.325 | 0.85 | 0.94 (0.78, 1.12) | 0.47 | 0.85 | 1.00 (0.87, 1.15) | 0.977 |
| FADS1        | rs174550  | T/C | 0.81 | 1.02 (0.82, 1.26) | 0.869 | 0.81 | 1.19 (1.00, 1.41) | 0.05 | 0.81 | 1.12 (0.98, 1.28) | 0.095 |
| GCK          | rs1799884 | A/G | 0.16 | 0.79 (0.62, 1.00) | 0.047 | 0.15 | 1.05 (0.88, 1.25) | 0.58 | 0.15 | 0.95 (0.82, 1.09) | 0.461 |
| DGK/TMEM195  | rs2191349 | T/G | 0.62 | 0.95 (0.79, 1.11) | 0.418 | 0.60 | 1.16 (1.02, 1.32) | 0.02 | 0.60 | 1.07 (0.97, 1.19) | 0.179 |
| PROX1        | rs340874  | C/T | 0.59 | 1.00 (0.84, 1.18) | 0.956 | 0.59 | 0.97 (0.85, 1.10) | 0.60 | 0.59 | 0.98 (0.88, 1.08) | 0.656 |
| G6PC2        | rs560887  | C/T | 0.82 | 0.97 (0.97, 1.33) | 0.084 | 0.84 | 0.89 (0.75, 1.06) | 0.19 | 0.84 | 1.00 (0.87, 1.14) | 0.993 |
| GLIS3        | rs7034200 | A/C | 0.48 | 0.96 (0.96, 1.35) | 0.837 | 0.48 | 1.18 (1.04, 1.34) | 0.01 | 0.48 | 1.16 (1.05, 1.29) | 0.003 |
| GCKR         | rs780094  | C/T | 0.74 | 0.87 (0.72, 1.05) | 0.139 | 0.72 | 1.07 (0.93, 1.23) | 0.35 | 0.73 | 0.99 (0.89, 1.11) | 0.883 |
| TCFT2L2      | rs7903146 | T/C | 0.31 | 1.25 (1.05, 1.49) | 0.014 | 0.32 | 1.22 (1.07, 1.40) | 0.00 | 0.32 | 1.23 (1.11, 1.37) | 0.000 |
| MADD         | rs7944584 | A/T | 0.77 | 1.01 (0.83, 1.23) | 0.893 | 0.78 | 1.12 (0.96, 1.31) | 0.15 | 0.78 | 1.08 (0.95, 1.22) | 0.230 |

UKADS = UK Asian Diabetes Study; DGP = Diabetes Genetics in Pakistan; Risk allele is the fasting glucose raising allele reported in Dupuis et al [1]; RAF = risk allele frequency, calculated using the normoglycaemic control groups.
The GCK rs1799884 SNP was used as a proxy for the rs4607517 variant reported in Dupuis et al [1].
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### Fasting Glucose Variants in South Asians

| Nearest Gene | SNP     | ES (95% CI)          | p     |
|--------------|---------|----------------------|-------|
| SLC30A8      | rs11558471 | 0.06 (0.01, 0.11)    | 1.50E-02 |
|              |         | 0.03 (0.02, 0.03)    | 5.50E-10 |
| GCK          | rs1799884 | 0.06 (-0.00, 0.12)   | 7.00E-02 |
|              |         | 0.08 (0.05, 0.07)    | 1.20E-04 |
| SLC2A2       | rs11920090| 0.04 (-0.03, 0.10)   | 2.45E-01 |
|              |         | 0.02 (0.01, 0.03)    | 3.30E-05 |
| GCKR         | rs780094  | 0.03 (-0.02, 0.08)   | 2.11E-01 |
|              |         | 0.03 (0.02, 0.03)    | 1.70E-24 |
| GLIS3        | rs7034200 | 0.02 (-0.02, 0.07)   | 2.91E-01 |
|              |         | 0.02 (0.01, 0.02)    | 1.20E-09 |
| FADS1        | rs174550  | 0.02 (-0.04, 0.08)   | 4.55E-01 |
|              |         | 0.02 (0.01, 0.02)    | 8.30E-09 |
| PROX1        | rs340874  | 0.02 (-0.03, 0.07)   | 3.64E-01 |
|              |         | 0.01 (0.01, 0.02)    | 6.60E-06 |
| TCF7L2       | rs7903146 | 0.02 (-0.03, 0.07)   | 4.44E-01 |
|              |         | 0.02 (0.02, 0.03)    | 2.80E-08 |
| ADRA2A       | rs10885122| 0.01 (-0.04, 0.07)   | 5.79E-01 |
|              |         | 0.02 (0.01, 0.03)    | 9.70E-08 |
| G6PC2        | rs560887  | 0.01 (-0.05, 0.08)   | 6.72E-01 |
|              |         | 0.08 (0.07, 0.08)    | 8.50E-122 |
| MADD         | rs7944584 | 0.00 (-0.05, 0.06)   | 9.12E-01 |
|              |         | 0.02 (0.02, 0.03)    | 5.10E-11 |
| CRY2         | rs11605924| 0.00 (-0.04, 0.06)   | 9.77E-01 |
|              |         | 0.01 (0.01, 0.02)    | 8.10E-08 |
| C2CD4B       | rs11071657| -0.01 (-0.05, 0.04)  | 7.66E-01 |
|              |         | 0.01 (0.00, 0.01)    | 1.00E-02 |
| ADCY5        | rs11708067| -0.01 (-0.06, 0.05)  | 7.81E-01 |
|              |         | 0.03 (0.02, 0.03)    | 1.70E-14 |
| MTNR1B       | rs10830963| -0.02 (-0.06, 0.03)  | 4.17E-01 |
|              |         | 0.07 (0.08, 0.07)    | 1.10E-102 |
| DGKB/TMEM195 | rs2191349 | -0.02 (-0.06, 0.03)  | 4.16E-01 |
|              |         | 0.03 (0.02, 0.04)    | 5.30E-29 |

acGRS        |         | 0.01 (0.00, 0.02)    | 4.60E-02 |
| wGRS         |         | 0.01 (-0.00, 0.02)   | 2.04E-01 |
Electronically, where the type 2 diabetes risk of the current study and the MAGIC study varied [1] and this heterogeneity achieved study-wide significance ($p = 1.29 \times 10^{-6}$). The acGRS showed a stronger association with fasting glucose than did the wGRS ($\beta = 0.015$ [95% CI: 0.000, 0.025] $p = 0.046$ and $\beta = 0.007$ [95% CI: $-0.004$, 0.018] $p = 0.204$ respectively) (Figure 1).

Associations with type 2 diabetes

None of the 16 studied variants displayed strong evidence for heterogeneity of effect on type 2 diabetes risk between the current study and the MAGIC study. In addition to the TCF7L2 and SLC30A8 variants, which have previously demonstrated association with type 2 diabetes in the UKADS/DGP study populations [3,6], alleles of the ADC15 rs11708067 [OR = 1.23 [95% CI: 1.09, 1.39] $p = 9.10 \times 10^{-6}$] and GLIS3 rs7034200 [OR = 1.16 [95% CI: 1.05, 1.29] $p = 3.49 \times 10^{-5}$] SNPs conferred risk of the disease in this study (Figure 2). The strength of these associations reached study-wide significance for the ADC15 variant; the GLIS3 SNP failed to reach this threshold by a narrow margin. Both risk score measures were associated with type 2 diabetes, with the wGRS displaying a stronger association (OR = 1.04 [95% CI: 1.02, 1.06] $p = 1.00 \times 10^{-6}$) than the acGRS (OR = 1.05 [95% CI: 1.02, 1.08] $p = 0.001$) (Figure 2). The strength of association of both risk scores was greatly attenuated by the removal of the previously associated TCF7L2 and SLC30A8 variants (wGRS: OR = 1.01 [95% CI: 0.90, 1.04] $p = 0.261$, acGRS: OR = 1.03 [95% CI: 1.00, 1.06] $p = 0.071$).

Discussion

In this study we investigated the effects of 16 SNPs on fasting glucose levels and type 2 diabetes risk in two South Asian populations of Punjab ancestry. Only the SLC30A8 rs11538471 variant was nominally associated with fasting glucose levels. Twelve of the 16 SNPs displayed positive $\beta$-values, however, suggesting that a number of these variants may be true determinants of fasting glucose levels in our study populations (Figure 1), even though their effects were too small to be accurately detected in our modestly-sized cohort. Comparing the effect sizes observed in this study to those reported in Europeans highlights some potential differences. Three of the six variants most strongly associated with fasting glucose in the MAGIC study [1][MTNR1B rs10830963, DGKB/TMEM195 rs2191349 and ADC15 rs11708067] have negative $\beta$-values in the current study (Figure 1), and this disparity reached statistical significance for the MTNR1B variant. The observed differences in effect size are probably the reason that the acGRS was nominally associated with fasting glucose levels, but the wGRS (weighted using European-derived $\beta$-values) was not.

It is of interest to note that variants within or near GCK, GCKR, G6PC2 and MTNR1B have been shown to be associated with fasting glucose levels in Indian Asians, with similar effect sizes to those seen in Europeans [9]. The GCK and GCKR SNPs studied in Indian Asians (rs4607519 and rs1260326 respectively) are in strong linkage disequilibrium (LD) with the SNPs genotyped in this
analyses in the Indian Asian study estimated that the strongest genotyped in the GIH HapMap samples. In addition, imputation CEPH collection) HapMap samples as rs10830963 has not been noted, however, that this LD estimate is taken from CEU (Utah residents with Northern and Western European ancestry from the described in both the Europeans from the MAGIC [1] study (Figure 1) and Indian Asians [9]. Although our estimate of effect size for the G6PC2 rs560887 variant is low (Figure 1), it is not statistically different from that seen in Europeans. In contrast, the MTNR1B rs10830963 variant displayed an effect size lower than that seen in Europeans, at study-wide significance. The MTNR1B variant reported as being associated with fasting glucose in Indian Asians [9] (rs2166706) is only in moderate LD (\(r^2 = 0.45\)) with the variant (rs10830963) genotyped in our South Asian cohort and reported as the sentinel MTNR1B SNP in the MAGIC study [1]; if different LD patterns result in rs2166706 being in tighter LD with the aetiological variant than rs10830963 in South Asians, this may explain some of the observed discrepancy in effect size. It must be noted, however, that this LD estimate is taken from CEU (Utah residents with Northern and Western European ancestry from the CEPH collection) HapMap samples as rs10830963 has not been genotyped in the GIH HapMap samples. In addition, imputation analyses in the Indian Asian study estimated that the strongest association signal for fasting glucose in this population was in fact the rs10830963 SNP [9], although this imputation was not able to utilise South Asian-specific LD patterns. It is interesting to note that a recent study of Indian Sikhs demonstrated that a low frequency variant (rs1374645) was associated with glucose levels, whereas rs10830963 was not [11]. Further studies of MTNR1B SNPs and their association with glucose levels in South Asians may be useful in fine-mapping the aetiological variant. Variants in TCF7L2 and SLC30A8 have previously been associated with type 2 diabetes in our Punjabi populations [3,6]. In addition to these variants, SNPs in ADCY5 and GLIS3 were associated with the disease in the current study. To our knowledge, this is the first time that either of these SNPs has been implicated in type 2 diabetes development in a South Asian population. The ADCY5 gene encodes adenylate cyclase 5, an enzyme that catalyses the generation of cAMP, a second messenger vital in a number of biological processes. It has been demonstrated in a large meta-analysis of Europeans that the rs11708067 SNP within ADCY5 is strongly associated (\(p<3.6 \times 10^{-8}\)) with type 2 diabetes, fasting glucose levels and HOMA-B (a measure of \(\beta\)-cell function) but is not associated with HOMA-IR (a measure of insulin resistance) [1,12]. This suggests that variants within this gene may exert their effect  

Table 3. Statistical power for fasting glucose and type 2 diabetes analyses in the combined UKADS/DGP study population.  

| Nearest gene | SNP          | South Asian RAF | MAGIC RAF | MAGIC effect size (OR) | Power | MAGIC effect size (mmol/l) | Power |
|--------------|--------------|-----------------|-----------|------------------------|-------|---------------------------|-------|
| MTNR1B       | rs10830963   | 0.40            | 0.30      | 1.09                   | 0.48  | 0.067                     | 0.75  |
| ADR4A        | rs10885122   | 0.76            | 0.67      | 1.04                   | 0.12  | 0.022                     | 0.12  |
| C2CD4B       | rs11071657   | 0.68            | 0.63      | 1.03                   | 0.09  | 0.008                     | 0.06  |
| SLC30A8      | rs11558471   | 0.73            | 0.68      | 1.15                   | 0.78  | 0.027                     | 0.16  |
| CRY2         | rs11605924   | 0.49            | 0.49      | 1.04                   | 0.14  | 0.015                     | 0.09  |
| ADCY5        | rs11708067   | 0.76            | 0.78      | 1.12                   | 0.57  | 0.027                     | 0.15  |
| SLC2A2       | rs11920090   | 0.85            | 0.87      | 1.01                   | 0.05  | 0.020                     | 0.09  |
| FADS1        | rs174550     | 0.81            | 0.64      | 1.04                   | 0.11  | 0.017                     | 0.08  |
| GCK          | rs1799884^a  | 0.15            | 0.16      | 1.07                   | 0.20  | 0.062                     | 0.43  |
| DGK/TMEM195  | rs2191349    | 0.60            | 0.52      | 1.06                   | 0.25  | 0.030                     | 0.22  |
| PROX1        | rs340887     | 0.59            | 0.52      | 1.07                   | 0.32  | 0.013                     | 0.08  |
| G6PC2        | rs560887^b   | 0.84            | 0.70      | 0.97                   | 0.08  | 0.075                     | 0.60  |
| GLIS3        | rs7034200    | 0.48            | 0.49      | 1.03                   | 0.10  | 0.018                     | 0.11  |
| GCKR         | rs800904     | 0.73            | 0.62      | 1.06                   | 0.21  | 0.029                     | 0.18  |
| TCF7L2       | rs7903146^c  | 0.32            | 0.31      | 1.40                   | 1.00  | 0.023                     | 0.14  |
| MADD         | rs7944584     | 0.78            | 0.75      | 1.01                   | 0.05  | 0.021                     | 0.11  |

RAF = risk (glucose-raising) allele frequency. Power was calculated using the South Asian RAF, the effect sizes reported in the MAGIC study [1], the sample sizes used in each analysis, an additive model and a significance level (\(z\)) of 0.05. For the type 2 diabetes analyses power calculations, a disease prevalence of 10% was assumed. For the fasting glucose analyses a population mean (SD) fasting glucose of 5.5 (0.6) mmol/l was used, as reported in Table 1.

^aIn the current study the GCK rs1799884 SNP was used as a proxy for the rs4607517 variant reported in MAGIC (\(r^2 = 1.0\) in CEU HapMap samples); the MAGIC RAF shown is for rs4607517.

^bFor the G6PC2 rs560887 SNP, the glucose-raising allele reduces the risk of type 2 diabetes (with nominal significance) in the MAGIC study. In this instance, to calculate power for the type 2 diabetes analysis the minor allele frequency (0.16) and the inverse of the odds ratio (OR; 1.03) was used.

^cThe RAF for the TCF7L2 rs7903146 SNP was not given in the MAGIC study; the RAF reported is for rs4506565 (\(r^2 = 0.92\) between the two variants in MAGIC).
effect on disease risk through .codigo_β-cell dysfunction and insulin secretion. In addition, a SNP within the ADIPT1 gene (rs9032904), in LD with the variant investigated in this study, is associated with foetal growth and birth weight [19]. Insulin is an important growth factor in utero, potentially providing a common mechanism linking reduced foetal growth with increased risk of type 2 diabetes. The GLIS3 gene encodes the transcription factor GLIS family zinc finger 3 isoform, a protein that regulates target gene transcription and has been shown to play a key role in β-cell generation in mice [14,15]. Rare functional mutations within the GLIS3 gene lead to a syndrome of neonatal diabetes and congenital hyperthyroidism [16], and the rs7020673 SNP within the gene is robustly associated with type 1 diabetes [17]. The GLIS3 rs7034200 SNP only displayed a weak association with type 2 diabetes in the MAGIC study [1], although there is evidence that this variant confers risk of the disease in a Chinese population [18]. As with the fasting glucose analyses, some potential disparity was apparent between our South Asian type 2 diabetes association results and those reported by the MAGIC study [1] (Figure 2), although the relatively small size of our cohort makes any differences difficult to quantify statistically. It is interesting to note that, excluding the TCF7L2 SNP, three of the four variants most strongly associated with type 2 diabetes in the MAGIC study [1] (MTNR1B rs10830963, PROX1 rs340874 and GCKR rs780094) have odds ratios of less than one in our South Asian populations (Figure 2).

The lack of association of many of the studied variants with fasting glucose and type 2 diabetes in our study cohort could be due to small sample size and low statistical power (Table 3). For the analysis of type 2 diabetes, this study had >80% power to detect the effect of just the TCF7L2 SNP. The study was underpowered to detect the effect of any SNP on fasting glucose levels, assuming similar effect sizes to those seen in European populations (Table 3). Although the statistical evidence for heterogeneity is weak, it is also possible that the studied variants have different effect sizes in our Punjabi populations compared with Europeans. This may be due to differences in LD patterns between the two ethnic groups, as disease-associated SNPs derived from GWAS studies are typically not aetiological variants. Previous findings that the MTNR1B and G6PC2 variants genotyped in this study are associated, either directly or through imputation, with glucose levels in Indian Asians [9], however, make it unclear whether any potential differences in LD patterns are likely to contribute to our observed lack of association at these loci.

In conclusion, our study of Punjab populations demonstrated that 12 of 16 variants displayed β-values for fasting glucose with the same direction of effect as that seen in Europeans. In addition, we provide evidence that alleles of SNPs in ADC15 and GLIS3 may confer risk of type 2 diabetes, the first time that this has been reported in South Asian populations.

Supporting Information

Table S1 Genotype distributions in the UKADS and DGP study populations.

(DOCX)

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Author Contributions

Conceived and designed the experiments: MAK. Performed the experiments: SDR. Analyzed the data: SDR. Wrote the paper: SDR MAK.

Contribution to discussion and reviewed/edited the manuscript: MZIH JPO SK ASS AB AHB.

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