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SHORT COMMUNICATION

Association of genetic predisposition to obesity with type 2 diabetes risk in Han Chinese individuals

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Abstract
Aims/hypothesis Obesity is a major risk factor for type 2 diabetes, but little is known about the contribution of BMI-associated loci to type 2 diabetes risk in East Asian populations.
Methods In this study, 30 known BMI-associated variants and a genetic risk score (GRS) calculated by summing the BMI-increasing alleles of these variants were tested for associations with type 2 diabetes and related glycaemic traits in 1,873 cases of type 2 diabetes and 1,839 controls in Han Chinese individuals. Logistic and linear regression analyses were performed to determine the association with type 2 diabetes risk or related glycaemic traits, respectively, under an additive model with or without adjustment for BMI.
Results The GRS was significantly associated with increased BMI (β [SE] 0.070 [0.016]; $p=1.33\times10^{-5}$) in the overall population. Each additional BMI-increasing allele in the GRS increased type 2 diabetes risk by 1.029-fold (95% CI 1.008, 1.050; $p=0.0056$) without adjustment for BMI, and the association was slightly attenuated after adjustment for BMI (OR 1.022; 95% CI 1.002, 1.043; $p=0.035$). In non-diabetic controls, the GRS was also associated with HOMA of beta cell function (HOMA-B) with adjustment for BMI (β [SE] −0.876 [0.345]; $p=0.011$). Notably, the association of GRS with type 2 diabetes was abolished after adjusting for HOMA-B (OR 1.012; 95% CI 0.986, 1.039; $p=0.380$).
Conclusions/interpretation Our results suggested that genetic predisposition to obesity leads to increased risk of type 2 diabetes, independent of BMI and partly through impaired beta cell function.

Keywords BMI · Chinese · Genetic risk score · HOMA-B · Type 2 diabetes

Abbreviations

GRS	Genetic risk score
GWAS	Genome-wide association study
HOMA-B	HOMA of beta cell function
HOMA-S	HOMA of insulin sensitivity
SNPs	Single-nucleotide polymorphisms

Introduction

Obesity is a major risk factor for type 2 diabetes. Genome-wide association studies (GWAS) have identified 38 loci convincingly associated with BMI in populations with

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European, Asian and African ancestry [1–3]. Recent studies in Europeans have demonstrated that the genetic susceptibility to obesity leads to increased risk of type 2 diabetes, through its obesity-increasing effect [4]. However, these studies did not include the most recently identified loci. Moreover, the BMI-associated loci may act differently in Asians and Europeans, since their adiposity phenotype and genetic background differ. For example, the *FTO* locus confers type 2 diabetes risk through its effect on BMI in Europeans, whereas in East Asians, the association remains after adjusting for BMI [5]. Therefore, it is of interest to test whether the genetic predisposition to obesity also contributes to type 2 diabetes risk through its effect on BMI in Han Chinese individuals. In this case–control study of 3,712 unrelated Han Chinese, we examined the association of a genetic risk score (GRS), based on 38 BMI-associated single-nucleotide polymorphisms (SNPs), with type 2 diabetes and glycaemic traits, and whether BMI mediated the association.

Methods

Study population Our analyses included 3,975 individuals (1,999 type 2 diabetes cases and 1,976 controls) from four studies. Full details of study populations, design, protocols and biochemical measurements have been described previously [6]. BMI was calculated as weight/height^2 (kg/m^2). Indices of insulin sensitivity (HOMA-S) and beta cell function (HOMA-B) were estimated by the homeostasis model using Levy's computer model (www.dtu.ox.ac.uk/homacalculator/download.php, 20 February 2014). The criteria for type 2 diabetes cases and non-diabetic controls are shown in the electronic supplementary material (ESM) Table 1. All studies were approved by local ethic committees, and informed written consent was obtained from all participants.

Genotyping After excluding the samples (n=263) who had call rate <97% and less than three SNPs with missing genotypes, 1,873 cases and 1,839 controls were included in this study (ESM Table 2). To date, 38 BMI-related loci have been identified in GWAS with $p<5\times10^{-8}$, of which eight are monomorphic in Han Chinese individuals [1–3]. Therefore, a total of 30 BMI-associated SNPs representing independent loci were included in this study. Even though the vast majority of these SNPs were first identified in populations of Europeans, most SNPs have also shown associations with BMI in East Asian populations [1, 2]. Yet, because of differences in linkage disequilibrium structure between East Asians and other ancestry populations, the selected SNPs may not always be the ones that show the strongest association in East Asians and thus could lower the statistical power. Genotyping and imputation have been described elsewhere [6]. Briefly, DNA samples were genotyped using the Illumina Human660W-Quad BeadChip (Illumina, San Diego, CA, USA). All genetic variants passed initial quality-control criteria with a call-rate ≥95% and genotype distribution in Hardy–Weinberg equilibrium ($p>1\times10^{-3}$). The IMPUTE software (version 2.1.2; http://mathgen.stats.ox.ac.uk/impute/impute.html) was used to impute SNPs from the phase 2 HapMap CHB+JPT (release 22) reference panel with high quality (Proper_info >0.8; ESM Table 3).

Statistical analyses Due to the non-normal distribution, values of insulin and HOMA-S were natural log-transformed before analyses. We calculated the unweighted GRS of each individual by summing the number of BMI-increasing alleles [1–3] of the 30 SNPs. The weighted GRS was calculated by weighting each BMI-increasing allele with the ratio of its reported β-coefficient to the sum of all SNPs' β-coefficients [1–3], and summing these values. Missing genotypes were replaced with the average BMI-increasing allele number for each SNP. Logistic and general linear regression models were applied to test the associations with type 2 diabetes risk and glycaemic traits, respectively, with adjustment for age, sex, region and BMI (where appropriate) under additive genetic model. The power calculations were performed using Quanto software (http://biostats.usc.edu/Quanto.html, version 1.2.4, May 2009) with minor allele frequencies and mean values of BMI from the current study and the effect sizes reported previously [1–3]. All p values were two-sided, with nominal significance defined as $p\leq0.05$. Bonferroni correction was used to adjust for multiple testing (i.e. five tests for the GRS and 150 tests for individual SNP analyses). As such, associations of which $p<0.01$ for GRS and $p<0.0003$ for single-SNPs were considered significant at a 5% α-level. Statistical analyses were performed in R version 2.15.0 (www.r-project.org/, 30 March 2012; University of Science and Technology of China, Hefei, China).

Results

The unweighted GRS was significantly associated with increased BMI in both non-diabetic controls (β [SE] 0.061 [0.022]; p=0.0059) and the whole samples (β [SE] 0.070 [0.016], $p=1.33\times10^{-5}$; ESM Fig. 1). Individually, 22 of the 30 SNPs showed directionally consistent associations with increased BMI in controls (p=0.0081 for binomial test), but only *LRRN6C*-rs10968576 showed significant association with BMI in the whole samples after Bonferroni correction (β [SE] 0.352 [0.090]; $p=8.98\times10^{-5}$; ESM Table 4).

Each additional BMI-increasing allele of the unweighted GRS was significantly associated with a 1.029-fold increased risk of type 2 diabetes (95% CI 1.008, 1.050; p=0.0056), adjusted for age, sex and region, and further adjustment for BMI only slightly attenuated the association (OR 1.022; 95%

Table 1 Association between the BMI GRS and risk of type 2 diabetes

Model	Unweighted GRS		Quantiles			
	OR (95% CI)	*p*	Q1	Q2	Q3	Q4
n (cases/controls)			559/584	422/462	427/401	465/391
Median (range)	29 (27–31)		26 (16–27)	28 (27–29)	30 (29–31)	32 (31–41)
Model 1[a]	1.029 (1.008–1.050)	0.0056[b]	1	0.949 (0.792–1.138)	1.100 (0.914–1.324)	1.258 (1.047–1.512)
Model 2[c]	1.022 (1.002–1.043)	0.035	1	0.903 (0.751–1.086)	1.074 (0.890–1.295)	1.196 (0.996–1.441)
Model 3[d]	1.012 (0.986–1.039)	0.380	1	0.883 (0.695–1.121)	1.039 (0.816–1.322)	1.134 (0.891–1.442)

[a] Model 1, adjusted for age, sex and region

[b] The associations remained significant after Bonferroni correction for multiple tests, and the Bonferroni corrected cut-off *p* value is 0.01 (0.05 divided by five tests)

[c] Model 2, adjusted for age, sex, region and BMI

[d] Model 3, adjusted for age, sex, region, BMI and HOMA-B

CI 1.002, 1.043; $p=0.035$; Table 1). Individually, BMI-increasing alleles of 21 SNPs were in the direction of associations with increased type 2 diabetes risk without adjustment for BMI ($p=0.021$ for binomial test) and four were nominally associated with increased type 2 diabetes risk (ESM Table 5). However, the BMI-increasing allele of *CDKAL1*-rs9356744 was significantly associated with decreased risk of type 2 diabetes (OR 0.72; 95% CI 0.66, 0.95; $p=2.63\times10^{-11}$) with or without adjustment for BMI (ESM Table 5). After removing the six SNPs that showed associations with type 2 diabetes individually, the association between the GRS and type 2 diabetes risk remained unchanged, suggesting that the association was not driven by one or a few loci.

The GRS was nominally associated with lower HOMA-B after adjusting for BMI (β [SE] −0.876 [0.345]; $p=0.011$; Table 2). Individually, eight SNPs showed nominal associations with glycaemic traits, but only the association between *GALNT10*-rs7708584 and HbA_{1c} value remained significant after Bonferroni correction (ESM Table 6). Notably, further adjustment for HOMA-B abolished the association between GRS and type 2 diabetes (OR 1.012; 95% CI 0.986, 1.039; $p=0.380$; Table 1) and excluding the participants who were receiving glucose-lowering treatment did not change the results (OR 1.01; 95% CI 0.93, 1.10; $p=0.79$). Similar results were observed for the weighted GRS (ESM Table 7). The triangular relationship between the GRS, BMI and type 2 diabetes also suggested that the association might be mediated through impaired beta cell function (ESM Fig. 2).

Discussion

In this type 2 diabetes case–control study of Han Chinese, we found that each additional BMI-increasing allele in the GRS was associated with about a 3% increased risk for type 2 diabetes, independent of BMI. In the non-diabetic controls, the BMI GRS was associated with lower HOMA-B after adjusting for BMI. The association of the GRS with type 2 diabetes was abolished after controlling for HOMA-B.

Similarly, previous studies in European populations have found that each additional BMI-increasing allele increased the OR of type 2 diabetes by 3–4% [4]. However, in Chinese Hans, unlike Europeans, the effect of GRS on type 2 diabetes seemed to be mediated by HOMA-B rather than by BMI. One

Table 2 Associations of BMI GRS with glycaemic traits in non-diabetic controls

Trait	Unweighted GRS	
	β (SE)	*p* value
BMI (kg/m^2)		
Model 1	0.061 (0.022)	0.0059[a]
Glucose (mmol/l)		
Model 1[b]	0.0013 (0.0025)	0.606
Model 2[c]	0.0006 (0.0025)	0.798
HbA_{1c} (%)		
Model 1[b]	0.0034 (0.0022)	0.116
Model 2[c]	0.0033 (0.0022)	0.137
Insulin (pmol/l)		
Model 1[b]	−0.0010 (0.0046)	0.833
Model 2[c]	−0.0034 (0.0045)	0.449
HOMA-B (%)		
Model 1[b]	−0.702 (0.348)	0.044
Model 2[c]	−0.876 (0.345)	0.011
HOMA-S (%)		
Model 1[b]	0.0007 (0.0045)	0.874
Model 2[c]	0.0032 (0.0044)	0.477

[a] The associations remained significant after Bonferroni correction for multiple tests, and the Bonferroni corrected cut-off *p* value is 0.01 (0.05 divided by five tests)

[b] Model 1, adjusted for age, sex, and region

[c] Model 2, adjusted for age, sex, region, and BMI

possible explanation for this discrepancy is that BMI might represent a somewhat different adiposity phenotype between Asians and white Europeans, since for a given BMI, East Asians and South Asians have a higher percentage of body fat than white Europeans. Moreover, due to differences in healthcare between China and western countries, it is possible that Chinese are diagnosed with type 2 diabetes at a later age. Consequently, they may have lost weight by the time of diagnosis and BMI may underestimate their adiposity level before the onset of type 2 diabetes.

Our results also showed that BMI GRS was nominally associated with decreased HOMA-B, which was independent of BMI. Moreover, analysis of the triangular relationship between the GRS, HOMA-B and type 2 diabetes, using GRS as an instrumental variable, also suggested that HOMA-B mediated, at least partially, the association between the GRS and type 2 diabetes. Although previous findings from GWAS of type 2 diabetes emphasised the importance of beta cell function in the development of type 2 diabetes [7], the exact mechanisms underlying the effects of the BMI loci on HOMA-B and type 2 diabetes remain unknown.

Individually, most SNPs showed directionally consistent effects on type 2 diabetes risk, as in Europeans [4], and only the BMI-increasing allele of *CDKAL1*-rs9356744 was significantly associated with decreased risk of type 2 diabetes. Consistently, a recent GWAS of BMI in East Asians also found that the BMI-decreasing allele of this SNP was associated with increased type 2 diabetes risk [1].

Our study had sufficient statistical power (≥80%) to detect associations of the GRS with BMI and type 2 diabetes risk, but it generally lacked power to replicate previously reported associations with BMI for most SNPs individually. Therefore, our primary analyses focus on the GRS analyses. Nevertheless, large-scale meta-analyses in East Asians have confirmed the single-SNP associations for most of the SNPs studied here [1, 2].

In summary, we concluded that the GRS for obesity also confers type 2 diabetes risk in Han Chinese individuals, and that its effect on type 2 diabetes is partly mediated through impaired beta cell function but is independent of BMI.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement JZ, LL, WG, GZ, RJFL, HL and XL contributed to the conception and design of the study. JZ, LL and WG carried out experiments. JZ, XY and LS interpreted the data. XL, HL, RH and LJ contributed to data acquisition and are the guarantors of this work, had full access to all the data, and take full responsibility for the integrity of data and the accuracy of data analysis. All authors were involved in writing the paper and had final approval of the submitted and published versions.

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