Association of the rs10830963 Polymorphism in *MTNR1B* with Fasting Glucose Levels in Chinese Children and Adolescents

Jie-Yun Song^{a,b*} Hai-Jun Wang^{a*} Jun Ma^c Zhi-Yuan Xu^{a,b} Anke Hinney^d
Johannes Hebebrand^d Yan Wang^a

^a Division of Maternal and Child Health, School of Public Health, Peking University Health Science Center,

^b Key Laboratory of Epidemiology, Ministry of Education,

^c Institute of Child and Adolescent Health, Peking University, Beijing, China

^d Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Essen, Germany

Keywords

MTNR1B · Glucose · Children · Adolescents

Summary

Aims: We aimed to identify whether the risk G-allele was associated with fasting glucose level and other pre-diabetic and obesity-related phenotypes in Chinese children and adolescents. **Methods:** The rs10830963 polymorphism in *MTNR1B* was genotyped in 2,030 Chinese children and adolescents of two independent studies. Association with fasting glucose levels and risk of impaired fasting glucose (IFG) were initially tested. Subsequently we analyzed the association with fasting insulin, homeostasis model assessment for insulin resistance (HOMA-IR) and for beta cell function (HOMA-B), the quantitative insulin sensitivity check index (QUICK) and obesity-related phenotypes (BMI standard deviation score, waist circumference etc.). **Results:** The G-allele of rs10830963 was associated with increased fasting glucose level in Chinese children and adolescents (increase of 0.072 mmol/l per G-allele, 95% CI 0.034–0.111, $p = 2.46 \times 10^{-4}$). The G-allele was also associated with an increased risk of IFG (OR = 1.21, 95% CI 1.00–1.46, nominal $p = 0.048$). We found the glucose-raising G-allele was nominally associated with reduced HOMA-B. No association to other pre-diabetic or obesity-related phenotypes was detected. **Conclusions:** The rs10830963 polymorphism in *MTNR1B* was associated with increased fasting glucose and risk of IFG in Chinese children and adolescents. The effect may result from reduced pancreatic beta cell function, but the mechanism awaits further studies.

Introduction

Melatonin was recently inferred to play an important role in the development of type 2 diabetes by influencing insulin secretion and endogenous glucose production [1]. The effect of melatonin is mediated by the membrane receptors, including melatonin receptor 1 (MT1, encoded by *MTNRI*A) and melatonin receptor 2 (MT2, encoded by *MTNR1*B). *MTNR1*B was found to be expressed in human retina, diencephalon, pancreatic islets and beta cells [2].

Among the variants identified to be associated with higher fasting glucose levels or the increased risk of type 2 diabetes by genome-wide association studies, common genetic variants within *MTNR1*B were associated with both phenotypes [2, 3]. The variant with the strongest association signal was the single nucleotide polymorphism (SNP) rs10830963, located in the single intron (11.5 kb) of *MTNR1*B. A meta-analysis revealed that rs10830963 is strongly associated with fasting glucose levels and moderately associated with an increased risk to develop diabetes [3]. The association with fasting glucose levels was replicated in several studies based on European populations [2, 4–9]. A study in non-diabetic individuals has identified an association of rs10830963 with impaired glucose-stimulated insulin secretion [4]. The risk allele was also related to impairment of early insulin secretion and beta cell dysfunction that might represent the pathomechanism for the increased risk of type 2 diabetes by the rs10830963 risk allele [3, 7]. Recently, the associations of rs10830963 with the elevated fasting glucose and risk of type 2 diabetes were reported in Asian adults, including Chinese [10–15], Japanese and Sri Lankan populations [16].

*Both authors contributed equally to this paper.

Concomitant with the obesity epidemic, the prevalence of type 2 diabetes in young individuals has raised worldwide [17]. Most studies of fasting glucose or type 2 diabetes focused on adults while there were limited studies among children and adolescents. Up to date, rs10830963 was reported to influence fasting glucose levels of children in some European studies [5, 9]. But there was only one related study in Chinese adolescents recently published during the review of our paper [12]. Whether the glucose-raising allele has similar effects in Asian children and adolescents need more studies. Therefore, we studied associations of rs10830963 with the pre-diabetic and obesity-related phenotypes in two independent study groups, including 2,030 Chinese children and adolescents aged 7–18 years.

Subjects and Methods

Subjects

We conducted an association study in two independent study groups recruited from the urban regions of Beijing, China. The first study group, including 386 obese, 400 overweight and 151 normal-weight individuals, came from the study on Adolescent Lipids, Insulin Resistance and Candidate Genes (ALIR) in nine middle schools of Dongcheng District of Beijing. The second study group, including 319 obese, 318 overweight and 456 normal-weight individuals, was from the Comprehensive Prevention Project for Overweight and Obese Adolescents (CPOOA) with physical exercise and healthy nutrition as instruments in five elementary and middle schools of the Haidian District of Beijing. The ascertainment strategies for the two study groups have been described in detail previously [18, 19]. We used the BMI percentile criteria for obese, overweight and normal-weight children and adolescents, which were determined in a representative Chinese population [20]. According to the criteria, the children and adolescents with an age- and gender-specific BMI greater or equal to the 95th percentile are defined as obese, while those with a BMI between 85th and 95th percentile are overweight and those with a BMI between 15th and 85th percentiles are normal weight. Individuals with any cardiovascular or metabolic disease were excluded. The two studies were approved by the ethic committee of Peking University Health Science Center. Written informed consent was provided by all participants and, in the case of minors, their parents. The general characteristics of the study groups are shown in table 1.

Anthropometric measurements, including height, weight, waist and hip circumferences, were determined according to standard protocols [18, 19]. Mean systolic and diastolic blood pressures were calculated by averaging three measurements. The skin fold thickness on the triceps, subscapula, abdomen and suprailium was measured. Fasting venous blood samples were taken for measurement of total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and fasting glucose using a biochemical auto-analyzer (Hitachi 7060, Tokyo, Japan). Fasting insulin was determined by the radio-immunoassay method (Beijing North Institute of Biological Technology, Beijing, China). We calculated the homeostasis model assessment of insulin resistance (HOMA-IR) and the homeostasis model assessment of pancreatic beta cell function (HOMA-B), by using the HOMA Calculator version 2.2 available from the Oxford Centre for Diabetes, Endocrinology and Metabolism (www.dtu.ox.ac.uk, accessed in March 2010) [21]. The quantitative insulin sensitivity check index (QUICK) was calculated according to the formula: $QUICK = 1/\log(\text{fasting insulin } (\mu\text{U/ml})) + \log(\text{fasting glucose (mmol/l)})$ [21]. The sex- and age-specific BMI standard deviation score (BMI-SDS) was calculated by using the growth reference data of the World Health Organization for children and adolescents aged 5–19 years [22].

Table 1. General characteristics of the study groups^a

	ALIR study				CPOOA study			
	normal-weight group	overweight group	obese group	p value	normal-weight group	overweight group	obese group	p value
Number	151	400	386	–	456	318	319	–
Female (%)	63 (41.72)	150 (37.5)	117 (30.31)	0.02	260 (57.02)	118 (37.11)	104 (32.60)	<0.001
Age, years	14.81 ± 0.75	14.63 ± 0.56	14.60 ± 0.55	0.001	11.80 ± 3.15	11.54 ± 2.63	10.73 ± 2.51	<0.001
Height, cm	166.80 ± 8.02	167.61 ± 7.68	170.41 ± 7.61	<0.001	152.69 ± 16.25	154.84 ± 14.67	153.45 ± 13.93	0.15
Weight, kg	56.87 ± 7.20	70.62 ± 7.13	87.47 ± 12.82	<0.001	43.86 ± 13.57	54.88 ± 14.72	62.37 ± 18.35	<0.001
BMI, kg/m ²	20.41 ± 1.83	25.08 ± 1.00	30.02 ± 3.07	<0.001	18.24 ± 2.46	22.33 ± 2.34	25.82 ± 3.64	<0.001
BMI-SDS	0.16 ± 0.67	1.59 ± 0.24	2.47 ± 0.44	<0.001	−0.05 ± 0.72	1.55 ± 0.30	2.52 ± 0.53	<0.001
Waist circumference, cm	69.40 ± 6.55	80.87 ± 4.78	93.05 ± 9.15	<0.001	63.15 ± 7.45	73.98 ± 7.90	82.20 ± 10.73	<0.001
Hip circumference, cm	89.99 ± 4.93	98.98 ± 3.99	107.18 ± 6.18	<0.001	80.17 ± 10.61	87.74 ± 9.67	92.847 ± 10.76	<0.001
Fasting glucose, mmol/l	4.44 ± 0.43	4.39 ± 0.63	4.45 ± 0.65	0.303	5.26 ± 0.38	5.40 ± 0.40	5.45 ± 0.40	<0.001
Fasting insulin ^b , μU/ml	0.74 ± 0.34	1.00 ± 0.33	1.15 ± 0.37	<0.001	1.08 ± 0.15	1.31 ± 0.07	1.35 ± 0.20	<0.001

ALIR study = Adolescent Lipids, Insulin Resistance and Candidate Genes; CPOOA study = Comprehensive Prevention Project for Overweight and Obese Adolescents; BMI-SDS = body mass index standard deviation score.

^aData are expressed as mean ± SD, if not indicated otherwise.

^bValues of fasting insulin were log₁₀-transformed; in the CPOOA study, fasting insulin were detected in a subgroup (the sample sizes of normal-weight, overweight and obese were 109, 2 and 160 respectively).

Genotyping

Genomic DNA was extracted from blood leukocytes by the phenol/chloroform extraction method. Genotyping of rs10830963 was carried out with tetra-primer amplification refractory mutation system analysis (tetra-primer ARMS-PCR) [23]. The sequences of primers were: F_{out}: 5'-TTT TTG TGC TGC AAA TGG GTT AAA GAG G-3'; R_{out}: 5'-GAG CCT TTG TTC AGA ACC ATG CTG CTT A-3'; F_{in}: 5'-CCA GTG ATG CTA AGA ATT CAC ACC ATG TG-3'; R_{in}: 5'-CCA GGC AG TTA CTG GTT CTG GAT TGG-3' (product size: G-allele (439 bp, 220 bp), C-allele (439 bp, 274 bp)). Different PCR products were clearly distinguished on 2.5% agarose gels stained with ethidium bromide. For reference ARMS-PCR of individuals with genotypes identified by sequencing were included in every run. For validity of genotypes, allele assignments were made by at least two experienced individuals independently. Discrepancies were solved unambiguously either by reaching consensus or by repeating. We genotyped 5% of samples twice for quality control and the genotyping concordance rate was 100%.

Statistics

The genotype data of the normal-weight group was tested for deviation from Hardy-Weinberg equilibrium with the χ^2 test. The relationships between rs10830963 polymorphism and quantitative variables (fasting glucose, fasting insulin, HOMA-B etc.) were tested by using the linear regression analysis with age, sex and study population as covariates. The values of fasting insulin, HOMA-B and HOMA-IR were log₁₀-transformed to address the skewness of distributions. Sensitivity analysis adjusting for BMI was also performed. Logistic regression analysis adjusted for age, gender and study population was used to calculate the odd ratio (OR) of the G-allele carriers for impaired fasting glucose levels. Additionally we used the linear regression analysis to compare the levels of obesity-related phenotypes of G-allele carriers with that of the non-carriers. All analyses were performed under an additive genetic model with the rs10830963 G-allele as the risk allele. For all variables, estimates and 95% confidence intervals (95% CIs) were calculated. Unless otherwise stated, all reported p values are nominal, two-sided and not adjusted for multiple testing. SPSS 10.0 software was used for the above statistical analyses (SPSS, Chicago, IL, USA). Revman 5.0 software (www.cc-ims.net/revman) was used to calculate standardized mean difference (SMD) of fasting glucose between different genotypes.

Results

The phenotypic characteristics of our study groups were shown in table 1. The age and gender differed by the obese subgroups in the two independent studies ($p < 0.05$). Weight, BMI, BMI-SDS, waist circumference, hip circumference and fasting insulin were significantly higher in overweight and obese groups than in their counterparts with normal weight ($p < 0.001$). The fasting glucose is significantly different by the obese subgroups in the CPOOA study ($p < 0.001$), but not in the ALIR study ($p = 0.303$).

We analyzed the rs10830963 genotype and phenotype data of 2,030 Chinese children and adolescents from two independent studies (ALIR and CPOOA). No deviation from Hardy-Weinberg equilibrium was observed in the normal-weight individuals of each study ($p = 0.724$ in ALIR and $p = 0.984$ in CPOOA). In total, 373 (18.37%) children and adolescents were homozygous carriers of the G-allele, 986 (48.57%) were heterozygous, and 671 (33.05%) were homozygous carriers of the C-allele. The G-allele frequency was 42.66%.

Applying an additive genetic model, we found a significant association between the rs10830963 G-allele and increased fasting glucose levels in both ALIR and CPOOA with the linear regression analysis adjusted for age and gender (both $p < 0.001$; table 2). We performed a combined analysis and confirmed the association ($p = 2.64 \times 10^{-4}$; table 3). The effect size of the G-allele on fasting glucose was 0.072 mmol/l (95% CI 0.034–0.111 mmol/l; table 3). The effect size did not change in the further analysis adjusted for BMI ($\beta = 0.076$ mmol/l, 95% CI 0.045–0.107 mmol/l; $p = 1.97 \times 10^{-6}$).

In addition, we tested whether there was a dominant effect of rs10830963 in our study population. The SMD of fasting glucose was 0.16 (95% CI 0.06–0.25) and 0.29 (95% CI 0.16–0.42) for CG versus CC and GG versus CC, respectively, confirming the additive effect of rs10830963.

The G-allele was also nominally associated with decreased HOMA-B levels (pancreatic beta cell function index) in the ALIR study group ($p = 0.037$) while there was no association to be observed in the CPOOA study group ($p = 0.490$; table 2). In the combined analysis, we found a nominally significant association of the G-allele with decreased HOMA-B ($p = 0.039$; table 3). The effect size of rs10830963 G-allele on fasting glucose decreased (0.068 mmol/l, 95% CI 0.024–0.112 mmol/l; $p = 0.003$) in the further analysis adjusted for HOMA-B. There was no association of the rs10830963 polymorphism with fasting insulin levels, HOMA-IR, or QUICK ($p > 0.40$).

According to the reference [24], we classified the children and adolescents into the group with impaired fasting glucose (IFG; fasting glucose being 5.6–6.9 mmol/l) and the normal-glucose group (fasting glucose < 5.6 mmol/l). In the combined analysis of the two independent studies, the frequency of the rs10830963 G-allele was higher in the IFG group than in the normal-glucose group (OR = 1.21, 95% CI 1.00–1.46, nominal $p = 0.048$; table 4).

The relationship between the rs10830963 and obesity-related phenotypes was also studied in the Chinese children and adolescents. The rs10830963 genotype frequencies of the overweight or obese group were not different from that of the normal-weight group ($p = 0.993$). We detected no significant association ($p > 0.30$; data not shown) for BMI, BMI-SDS, waist circumference, hip circumference, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure as well as the skin fold thickness on triceps, subscapula, abdomen and suprailium.

Discussion

The common genetic variant rs10830963 in *MTNR1B* was reported to be associated with increased fasting glucose levels in several populations [5, 9]. We found a significant association of the G-allele of rs10830963 in *MTNR1B* with fasting glucose levels using an additive model, with the effect size of 0.076

Table 2. The relationship between the rs10830963 polymorphism and fasting glucose, insulin, indices of insulin resistance or sensitivity in two independent studies of Chinese children

Genotype	ALIR study		CPOOA study			
	n	mean ± SD	effect size (95% CI) ^a	p value ^a	n	mean ± SD effect size (95% CI) ^a p value ^a
Fasting glucose, mmol/l						
CC	304	4.34 ± 0.61			367	5.30 ± 0.41
CG	458	4.42 ± 0.59			528	5.37 ± 0.40
GG	175	4.55 ± 0.65	0.097 (0.042–0.153)	6.09 × 10 ⁻⁴	198	5.40 ± 0.39
						0.057 (0.024–0.090) 7.91 × 10 ⁻⁴
Fasting insulin ^b , μU/ml						
CC	297	1.04 ± 0.35			95	1.24 ± 0.25
CG	446	1.02 ± 0.40			131	1.25 ± 0.21
GG	170	1.03 ± 0.36	-0.012 (-0.046 to 0.023)	0.514	45	1.23 ± 0.23
						-0.008 (-0.046 to 0.030) 0.693
HOMA-B ^b						
CC	297	2.25 ± 0.25			95	2.21 ± 0.16
CG	446	2.22 ± 0.28			131	2.21 ± 0.14
GG	170	2.20 ± 0.26	-0.026 (-0.051 to -0.002)	0.037	45	2.20 ± 0.16
						-0.009 (-0.033 to 0.016) 0.49
HOMA-IR ^b						
CC	297	0.19 ± 0.34			95	0.40 ± 0.24
CG	445	0.17 ± 0.38			131	0.42 ± 0.20
GG	170	0.18 ± 0.35	-0.008 (-0.041 to 0.026)	0.658	45	0.40 ± 0.22
						-0.005 (-0.042 to 0.031) 0.768
QUICK						
CC	297	0.63 ± 0.17			95	0.52 ± 0.07
CG	446	0.64 ± 0.38			131	0.51 ± 0.06
GG	170	0.63 ± 0.18	0.002 (-0.025 to 0.029)	0.899	45	0.52 ± 0.06
						0.0004 (-0.010 to 0.011) 0.938

ALIR study = Adolescent Lipids, Insulin Resistance and Candidate Genes; CPOOA study = Comprehensive Prevention Project for Overweight and Obese Adolescents; HOMA-IR = homeostasis model assessment of insulin resistance; HOMA-B = homeostasis model assessment of pancreatic beta cell function; QUICK = the quantitative insulin sensitivity check index.

^ap values and effect sizes were calculated by using the linear regression analysis adjusted for age and sex.

^bValues of fasting insulin, HOMA-IR and HOMA-B were log₁₀-transformed.

Table 3. The relationship between the rs10830963 polymorphism and fasting glucose, fasting insulin, indices of insulin resistance or sensitivity in the combined analyses of 2,030 Chinese children

Genotype	N	Mean ± SD	Effect size ^a (95% CI)	P value ^a
Fasting glucose, mmol/l				
CC	671	4.87 ± 0.70	0.072 (0.034–0.111)	2.64 × 10 ⁻⁴
CG	986	4.93 ± 0.69		
GG	373	5.00 ± 0.68		
Fasting insulin ^b , μU/ml				
CC	392	1.09 ± 0.34	−0.008 (−0.036 to 0.020)	0.581
CG	577	1.07 ± 0.37		
GG	215	1.07 ± 0.35		
HOMA-B ^b				
CC	392	2.24 ± 0.23	−0.021 (−0.041 to −0.001)	0.039
CG	576	2.22 ± 0.25		
GG	215	2.20 ± 0.24		
HOMA-IR ^b				
CC	392	0.24 ± 0.35	−0.004 (−0.032 to 0.023)	0.75
CG	577	0.23 ± 0.36		
GG	215	0.23 ± 0.34		
QUICK				
CC	392	0.60 ± 0.16	0.001 (−0.020 to 0.022)	0.956
CG	577	0.61 ± 0.34		
GG	215	0.61 ± 0.17		

HOMA-IR = Homeostasis model assessment of insulin resistance; HOMA-B = homeostasis model assessment of pancreatic beta cell function; QUICK = the quantitative insulin sensitivity check index.

^a P values and effect sizes were calculated by using the linear regression analysis adjusted for age, sex and study population.

^b Values of fasting insulin, HOMA-IR and HOMA-B were log₁₀-transformed.

Table 4. The association of the rs10830963 polymorphism with impaired fasting glucose in the combined analysis of 2,030 Chinese children

	Genotype, n (%)			Adjusted OR (95% CI) ^a	P value ^a
	CC	CG	GG		
Normal glucose group	583 (33.5)	849 (48.7)	310 (17.8)	Reference	0.048
Impaired fasting glucose group	88 (30.6)	137 (47.6)	63 (21.9)	1.21(1.00–1.46)	

^a Odds ratio (OR) with 95% CI and p value were estimated with logistic regression analysis adjusted for age, sex and study population.

mmol/l per G-allele. The result was consistent with previous studies on European children and adolescents [5, 9]. Kelliny et al. [5] observed that the G-allele of rs10830963 was positively associated with fasting glucose levels (β = 0.069 mmol/l) in 2,025 healthy children and adolescents from the European Youth Heart Study (EYHS) in Estonia and Denmark (age range 9–11 and 14–16 years). Sparso et al. [9] replicated the effect in 5,258 children aged 16 years of the Northern Finland 1986 Birth Cohort (NFBC86), with the increase of fasting glucose being 0.060 mmol/l per G-allele.

We additionally found that the association between rs10830963 G-allele and fasting glucose levels was unaltered after adjustment for BMI, which is in line with the previous

studies [3, 5]. Our data indicated that the genetic variant contributed to elevated fasting glucose levels independently of the degree of adiposity as it had been shown in European populations [3, 5]. The effect sizes in children of different ethnic background were similar. However, we observed that the G-allele frequency in Chinese children and adolescents was 43%, which is similar to Chinese adults (42%), but higher than the frequency in European populations (20–34% [3]). As more Chinese people carry the risk allele of rs10830963, it was suggested that its effect on fasting glucose levels should be paid more attention in Asia.

There was a study in Chinese adolescents recently published during the review of our paper (abbreviated as PMID

20628598) [12]. Our study not only replicated its findings but also provided more interesting findings:

- i) The association of rs10830963 and fasting glucose was more significant in our study with $p = 2.64 \times 10^{-4}$ compared to $p = 0.0475$ in PMID 20628598. The reason might be that our study involved two independent cohorts from north China, having larger sample size (2,030 in our study, 1,061 adolescents in PMID 20628598).
- ii) Our study population was different from PMID 20628598, including wider age range (children and adolescent aged 7–18 years in our study, adolescents with mean age 15.4 ± 1.9 years in PMID 20628598), and different BMI levels (23.8 ± 4.8 kg/m² in our study, 19.9 ± 3.5 kg/m² in PMID 20628598). The results of our study will provide more evidences for the role of rs10830963.
- iii) In the PMID 20628598 study, weaker and dominance effects of rs10830963 were found in Chinese, with SMD of fasting glucose being 0.20 (95% CI 0.11–0.28) and 0.23 (95% CI 0.12–0.34) for CG versus CC and GG versus CC, respectively, which was different from the additive effect in Europeans. We performed a similar analysis in our study population, but did not find any dominant effect. In a recent meta-analysis, the overall effect size on fasting glucose among Asians tended to be smaller than that in white Europeans, but the heterogeneity observed in white Europeans may introduce bias [11]. Whether there is ethnic difference for the role of rs10830963 awaits more studies.

Moreover, we found the association of the G-allele at rs10830963 with increased risk of IFG in children and adolescents which confirmed a recent study in middle-aged Danes [9]. Girls of Caucasian and African decent aged 9–10 years with IFG were shown to be at a greater risk to develop type 2 diabetes a decade later [25]. In a study of Israelian young men, higher fasting glucose levels within the normal glycemic range were an independent risk factor for type 2 diabetes [26]. Therefore, the identification of fasting glucose gene variants in children and adolescents will be useful for screening of glucose disorder and preventing diabetes at an early age.

We also found that the G-allele of rs10830963 that leads to increased glucose level was associated with reduced pancreatic beta cell function (HOMA-B) in the ALIR study and the combined analysis. But the polymorphism had no significant effect on fasting insulin, insulin resistance (HOMA-IR) or insulin sensitivity (QUICK). The effect size of rs10830963 G-allele on fasting glucose decreased in the further analysis adjusted for HOMA-B. If our observed association between rs10830963 and HOMA-B is replicated in multiple cohorts, it might be possible that the increase in fasting glucose levels by the G risk allele of rs10830963 might be due to impaired pancreatic beta cell function. Some previous studies reported that the G-allele of rs10830963 was associated with decreased insulin release response to oral and intravenous glucose challenge, reduced glucose-stimulated early phase insulin

secretion and decreased beta cell glucose sensitivity [4, 6, 7]. Langenberg et al. [6] further recognized that the defect of pancreatic beta cell function remained significant after accounting for the whole-body insulin sensitivity level during oral glucose tolerance test. Since the *MTNR1B* gene is predominantly expressed in pancreatic beta cells, the direct regulation of beta cell function was supposed to be an important pathway for the increased fasting glucose effect of rs10830963. However, the role of the polymorphism in the etiology of type 2 diabetes was not clear. Being located in the single intron of *MTNR1B*, the rs10830963 may not disrupt consensus transcription factor binding or cryptic alternative splice sites [3]. But the level of *MTNR1B* mRNA in pancreatic islets was observed to be higher in the G-allele carriers than that in the non-carriers among non-diabetics older than 45 years [7]. How the rs10830963 influences the expression of *MTNR1B* awaits further functional studies.

No association between the G-allele of rs10830963 and reduced HOMA-B was observed in the CPOOA study, partly due to the small size of the fasting insulin subgroup. It was also reported that the effect of the G-allele on HOMA-B is marginally stronger at a later pubertal stage than at an earlier stage [5]. In the PMID 20628598 study [12], rs10830963 was found to be associated with HOMA-B ($p = 0.0042$) in adolescents (15.4 ± 1.9 years). In our study the association was observed in the ALIR study, but not in the CPOOA study. We considered that the age range of the children and adolescents in the CPOOA study (7–18 years) was wider than that in the ALIR study (14–17 years), which may also have contributed to the non-significant association of rs10830963 polymorphism with HOMA-B. It was reported that the effect of the G-allele on HOMA-B is marginally stronger at a later pubertal stage than at an earlier stage [5]. The HOMA-B result of our study was interesting when it was considered together with that of the PMID 20628598 study, suggesting that the role of rs10830963 might vary in different pubertal stages. In addition, we extended the association study of rs10830963 to BMI, BMI-SDS as well as other obesity-related phenotypes. However, associations were not detected. Staiger et al. [4] had similar results for BMI, body fat content and waist circumference. Since fasting glucose was associated with BMI in the CPOOA study, the SNP was not associated with BMI making it less likely for BMI to be confounding the association between the SNP and fasting glucose. However, further studies in larger populations are necessary to clarify the role of rs10830963 in the development of obesity.

In conclusion, we found the G-allele at rs10830963 in *MTNR1B* was associated with increased fasting glucose, the risk of IFG and decreased HOMA-B in Chinese children and adolescents. The polymorphism might affect pancreatic beta cell function so as to reduce insulin secretion, resulting in impaired fasting glucose, but the mechanism awaits further studies.

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Disclosure Statement

The authors declared no conflict of interest.

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