

## Article

### **Common polymorphism near the *MC4R* gene is associated with type 2 diabetes: data from a meta-analysis of 123,373 individuals**

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## **Abstract**

*Aims/hypothesis* Genome-wide association studies have shown that variants near the melanocortin 4 receptor gene (*MC4R*) (rs17782313 and rs12970134) are associated with risk of obesity in Europeans. As obesity is associated with an increased risk of type 2 diabetes, many studies have investigated the association between polymorphisms near the *MC4R* gene and type 2 diabetes risk across different ethnic populations, with inconsistent results. In this study, we performed a meta-analysis to clarify the association of variants near *MC4R* with type 2 diabetes risk.

*Methods* Published literature from PubMed and Embase was retrieved. All studies that evaluated the association of at least one of the two *MC4R* polymorphism(s) with type 2 diabetes were included in the study. Pooled ORs with 95% CIs were calculated using the fixed-effects model.

*Results* A total of 19 studies (comprising 34,195 cases and 89,178 controls) of the rs17782313 polymorphism (or its proxy rs12970134) were included in the meta-analysis. The results indicated that the rs17782313 polymorphism was significantly associated with type 2 diabetes risk among the overall study population (OR 1.10, 95% CI 1.07, 1.13,  $p = 2.83 \times 10^{-12}$  [Z test],  $I^2 = 9.1\%$ ,  $p = 0.345$  [heterogeneity]). The association remained significant even after adjustment for body mass index (BMI) (OR 1.06, 95% CI 1.03, 1.09,  $p = 2.14 \times 10^{-5}$  [Z test],  $I^2 = 4.9\%$ ,  $p = 0.397$  [heterogeneity]). Further sensitivity analysis confirmed the statistically significant association of rs17782313 polymorphism with type 2 diabetes, and no publication bias was detected.

*Conclusions/interpretation* The present meta-analysis confirmed the significant association of the rs17782313 polymorphism near the *MC4R* gene with type 2 diabetes risk, which was independent of BMI.

## **Keywords:**

*MC4R*, Meta-analysis, Obesity, Polymorphism, Type 2 diabetes

**Abbreviations:**AGEN-T2D, Asian Genetic Epidemiology Network–Type 2 Diabetes

DIAGRAM, Diabetes Genetics Replication And Meta-analysis

FTO, Fat-mass- and obesity-associated

GWAS, Genome-wide association study

LD, Linkage disequilibrium

MC4R, Melanocortin 4 receptor

SNP, Single nucleotide polymorphism

## Introduction

Type 2 diabetes is one of the main health issues worldwide. It is a complex disease that involves genetic and environmental factors and their interactions. Many studies have indicated that obesity increases the risk of type 2 diabetes [1]. However, the mechanism underlying the association between obesity and type 2 diabetes remains unclear and it is possible that these features share a common genetic background.

Recent genome-wide association studies (GWASs) have identified many single nucleotide polymorphisms (SNPs) that are significantly associated with obesity [2-6]. Of these, the fat mass and obesity-associated gene (*FTO*) shows the largest effect. In 2007, Frayling et al [2] found that the significant association between rs9939609 polymorphism in *FTO* and type 2 diabetes was abolished after adjustment for BMI (crude OR 1.15, 95% CI 1.09, 1.23; after adjustment for BMI, OR 1.03, 95% CI 0.96, 1.10), suggesting that the effect of the *FTO* variant on type 2 diabetes risk in Europeans is mediated through BMI. However, a recent large meta-analysis comprising 96,551 individuals demonstrated that the *FTO* polymorphism was significantly associated with type 2 diabetes independent of BMI among East and South Asians (crude OR 1.15, 95% CI 1.09, 1.21; after adjustment for BMI, OR 1.10, 95% CI 1.05, 1.16) [7].

In 2008, variants near the melanocortin 4 receptor gene (*MC4R*) (rs17782313 and rs12970134) were reported as the second association signal for BMI/obesity by two GWASs [3, 4]. The association was subsequently confirmed by other GWASs [5, 6]. As obesity is associated with an increased risk of type 2 diabetes, many studies have investigated the association between polymorphism near the *MC4R* gene and type 2 diabetes risk across different ethnic populations; however, the results have been inconsistent [3, 6, 8-16]. In this study, a systematic meta-analysis was performed to clarify the association between polymorphism(s) near the *MC4R* gene and the risk of type 2 diabetes.

## Methods

*Literature and search strategy* We searched literature databases, including PubMed and

Embase. The search strategy was to identify all possible studies involving the following key words: (melanocortin 4 receptor gene or *MC4R*) and (polymorphism or variant or variation) and (type 2 diabetes or T2D). The publication language was restricted to English. The reference lists of retrieved articles were hand-searched. If more than one article was published using the same case series, only the study with the largest sample size was included. The literature search was updated on 25 March 2012. We also investigated the association of the *MC4R* rs17782313 variant with type 2 diabetes in two large GWAS consortia belonging to two different ethnicities: the Diabetes Genetics Replication And Meta-analysis (DIAGRAM) consortium (11275 cases and 11275 controls of European ancestry) [17]; and the Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) consortium (6952 cases and 11865 controls of East Asian ancestry) [18].

*Inclusion criteria and data extraction* The studies were included in the meta-analysis only if they met all the following inclusion criteria: (1) evaluation of the association of *MC4R* polymorphism(s) (rs17782313 and/or rs12970134) with type 2 diabetes; (2) use of a case–control or cohort design; and (3) provision of an OR with 95% CI under an additive model or sufficient data for calculation of this estimate. The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country of origin; (4) ethnicity of the studied population; (5) study design; (6) number of cases and controls; (7) frequency of men and the mean ages; (8) mean BMI; and (9) studied SNPs. Two authors independently reviewed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision. All participants of the included studies provided informed consent and the studies were approved by the ethics committees of the participating institutions.

*Statistical analysis* The association of *MC4R* polymorphism with type 2 diabetes was estimated by calculating the pooled OR and 95% CI. The significance of the OR was

determined by the Z test ( $p < 0.05$  was considered statistically significant). Cochrane's  $Q$  test was performed to test the between-study heterogeneity. A random-effects (DerSimonian–Laird) or fixed-effects (Mantel–Haenszel) model was used to calculate the pooled OR in the presence ( $p \leq 0.10$ ) or absence ( $p > 0.10$ ) of heterogeneity, respectively. Publication bias was assessed by Begg's test and Egger's test ( $p < 0.05$  was considered statistically significant). To evaluate the stability of the results, we performed a sensitivity analysis by removing one study at a time. Data were analysed using STATA version 11.0 (StataCorp LP, College Station, TX, USA).

## Results

*Characteristics of the studies* A flow chart describing the process of inclusion/exclusion of study is presented in Fig. 1. The literature search identified a total of 73 potentially relevant articles. Of these, 50 were excluded after reading the title or abstract because of obvious irrelevance e.g. experimental articles and functional research. In addition, one article was excluded as it was a review and nine articles were excluded because they investigated the association between the *MC4R* polymorphism and obesity, obesity-related traits, stroke or polycystic ovary syndrome. Therefore, 13 articles met the primary inclusion criteria, of which one article was excluded because it was a duplicated publication [19] and another article was excluded because it did not provide sufficient data for calculation of an OR with 95% CI [20]. In addition, the nine studies included in the paper by Loos et al [3] were considered as separate studies in the following data analysis. The variant rs17782313 is known to be in high linkage disequilibrium (LD) with rs12970134 ( $D' = 0.95$ ,  $r^2 = 0.82$  in CEU (Utah residents with Northern and Western European ancestry from the CEPH collection);  $D' = 0.902$ ,  $r^2 = 0.813$  in CHB (Han Chinese in Beijing, China);  $D' = 0.911$ ,  $r^2 = 0.662$  in JPT (Japanese in Tokyo, Japan)). Because of the high LD, we could not clarify which of the two SNPs is primarily associated with type 2 diabetes. In addition, if any study analysed both polymorphisms, only the rs17782313 polymorphism was selected.

A total of 19 studies (comprising 34,195 cases and 89,178 controls) for rs17782313 (or its proxy rs12970134) polymorphism were included in the meta-analysis [3, 6, 8-16]. Of these, 14 studies involved Europeans, four were of East Asians, and one involved South Asians. The genotype frequency in controls was in Hardy–Weinberg equilibrium for all included studies ( $p>0.05$ ). All studies (except for the study by Huang et al [14]) provided the crude and adjusted ORs with 95% CIs (adjusted for BMI), and the majority provided ORs with 95% CIs under an additive genetic model, hence we calculated the summary estimate under this model only [7]. The characteristics of the included studies are listed in Table 1.

*Meta-analysis results* The results showed a significant association of the rs17782313 polymorphism near the *MC4R* gene with the risk of type 2 diabetes (OR 1.10, 95% CI 1.07, 1.13,  $p=2.83\times10^{-12}$  [Z test],  $I^2=9.1\%$ ,  $p=0.345$  [heterogeneity], Fig. 2a), which retained significance even after adjustment for BMI (OR 1.06, 95% CI 1.03, 1.09,  $p=2.14\times10^{-5}$  [Z test],  $I^2=4.9\%$ ,  $p=0.397$  [heterogeneity], Fig. 2b). The results were similar in subgroups of Europeans and East Asians (electronic supplementary material [ESM] Fig. 1a and ESM Fig.1b).

*Sensitivity analysis* Sensitivity analysis was performed by excluding one study at a time. The results confirmed the significant association between the rs17782313 polymorphism near the *MC4R* gene and the risk of type 2 diabetes, with ORs and 95% CIs ranging from 1.09 (1.06, 1.12) to 1.11 (1.08, 1.14), and from 1.05 (1.02, 1.09) to 1.09 (1.05, 1.12) after adjustment for BMI.

*Publication bias* We did not observe any publication bias for the rs17782313 polymorphism (Begg's test  $p=0.726$ , Egger's test  $p=0.872$ ; after adjustment for BMI, Begg's test  $p=0.820$ , Egger's test  $p=0.687$ ).

*Analysis in two GWAS consortia* Replication analysis of our observations from a



meta-analysis of GWAS consortia showed that rs17782313 polymorphism was associated with type 2 diabetes in both Europeans (OR 1.06, 95% CI 1.01, 1.11,  $p=0.022$  [Z test]) and in East Asians (OR 1.11, 95% CI 1.05, 1.18,  $p=1.95\times 10^{-4}$  [Z test]). This association remained significant in East Asians even after adjustment for BMI (OR 1.08, 95% CI=1.01, 1.14,  $p=0.016$  [Z test]). However, the analysis of influence of BMI adjustment on association between rs17782313 polymorphism and type 2 diabetes in Europeans could not be performed because BMI data were unavailable for the DIAGRAM consortium.

## Discussion

In the last few years, several GWASs have been carried out for type 2 diabetes and have identified close to 60 loci associated with type 2 diabetes. However, none has reported the SNPs investigated in the present study as strong markers of type 2 diabetes risk. To our knowledge, this is the first meta-analysis investigating the association between polymorphisms near the *MC4R* gene and type 2 diabetes susceptibility across different ethnic populations. Our meta-analysis, comprising 123,373 individuals from different ethnicities, confirmed that the variant near the *MC4R* gene was significantly associated with an increased risk of type 2 diabetes and the association remained significant even after adjustment for BMI. This observation is further strengthened by the independent observation from two large GWAS consortia from contrasting ethnicities. Despite differences in the genetic backgrounds of Europeans and East and South Asians, there was no heterogeneity in the overall population and the effect sizes were similar in Europeans and East Asians.

The *FTO* gene was one of the first loci identified for type 2 diabetes risk by GWAS in Europeans. However, after adjustment for BMI, the association with type 2 diabetes completely disappeared. Most recently, a large-scale meta-analysis by Li et al [7] demonstrated a significant association between a variant of the *FTO* gene and the risk of type 2 diabetes in East and South Asians. Notably, after adjustment for BMI, the association remained, suggesting that the *FTO* gene influenced the risk of type 2 diabetes independently of BMI. Similarly, we also observed the significant association between polymorphism near

the *MC4R* gene and type 2 diabetes independent of BMI in European and Asian populations.

The mechanism underlying the association of the *MC4R* polymorphism with type 2 diabetes risk remains unknown. Like the fat-mass- and obesity-associated (*FTO*) protein, melanocortin 4 receptor (*MC4R*) protein is produced in abundance in the central nervous system, which regulates energy metabolism [5]. Many studies have indicated that *MC4R* may influence both food intake and energy expenditure through a distinct pathway [21]. On the other hand, our results are in agreement with the finding that *MC4R* polymorphism is significantly related to insulin resistance [4]. Further longitudinal studies are necessary to investigate the independent effect of the *MC4R* gene and its interaction with obesity on risk of type 2 diabetes.

In conclusion, our meta-analysis confirmed the BMI-independent significant association of rs17782313 polymorphism near the *MC4R* gene with risk of type 2 diabetes in the study population comprising Europeans and Asians. These findings are similar to those showing an association of *FTO* variants with type 2 diabetes risk in Asians [7]. Further studies should be conducted to identify the causal variant and the underlying mechanism of the identified association.

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**Contribution statement**

BX and JM conceived and designed the study. FT, GRC, NK, HWP, HYP and DHZ contributed to acquisition, analysis and interpretation of data. BX and GRC drafted the article. BX, JM, GRC, NK, HWP, HYP and DHZ revised the article critically for important intellectual content. All authors approved the final version to be published.

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

**Table 1** Characteristics of individual studies included in the meta-analysis

Authors [ref]	Country	Ethnicity	Study design	Sample size		Sex (% men)	Age (Mean [SD], years)	BMI (Mean [SD], kg/m2)	MC4R SNP
				Cases	Controls				
Loos et al (2008) (EPIC-Obesity) [3]	UK	European	Population based	192	2223	47.3	59.2 (9.0)	26.4 (3.9)	rs17782313
Loos et al (2008) (British 1958 BC) [3]	UK	European	Population based	111	1368	50.0	44.5 (2.5)	27.4 (4.8)	rs17782313
Loos et al (2008) (CoLaus) [3]	Switzerland	European	Population based	428	5205	47.0	53.2 (10.8)	25.8 (4.6)	rs17782313
Loos et al (2008) (EPIC-Norfolk) [3]	UK	European	Population based	725	15890	49.0	58.8 (9.3)	26.3 (3.8)	rs17782313
Loos et al (2008) (MRC-Ely) [3]	UK	European	Population based	139	1558	46.0	61.1 (9.1)	27.2 (4.8)	rs17782313
Loos et al (2008) (Dundee case-control 1) [3]	UK	European	Case-control	2022	2037	Cases: 58.0	Cases: 64.2 (9.4)	Cases: 31.5 (6.0)	rs17782313
						Controls: 51.0	Controls: 58.7 (12.0)	Controls: 26.6 (4.4)	
Loos et al (2008) (Dundee case-control 2) [3]	UK	European	Case-control	1103	1559	Cases: 54.0	Cases: 63.7 (9.9)	Cases: 31.8 (6.4)	rs17782313
						Controls: 53.0	Controls: 59.0 (11.8)	Controls: 26.9 (4.5)	
Loos et al (2008) (YT2D-OXGN - EFSOCH case-control) [3]	UK	European	Case-control	632	1750	Cases: 59.0	Cases: 59.2 (8.6)	Cases: 32.1 (6.3)	rs17782313
						Controls: 49.0	Controls: 31.6 (5.8)	Controls: 25.3 (4.4)	
Loos et al (2008) (WTCCC/T2DM	UK	European	Case-control	1924	1485	Cases: 58.0	Cases: 58.56 (10.14)	Cases: 31.2 (6.1)	rs17782313

case-control) [3]									
						Controls: 48.0	Controls: 43.4 (12.3)	Controls: 26.2 (4.3)	
Qi et al (2008) [8]	USA	European	Case-control	1533	4191	All were women	54.1 (6.7)	Not reported	rs17782313
Cauchi et al (2009) [9]	France	European	Cohort	307	2351	Cases: 70.0	Cases: 61.6 (8.7)	Cases: 29.1 (4.6)	rs17782313 <sup>a</sup>
						Controls: 43.0	Controls: 54.4 (9.7)	Controls: 24.9 (3.8)	
Zobel et al (2009) [10]	Denmark	European	Case-control	3903	4918	49.6	46.0 (8.0)	26.1 (4.5)	rs17782313 <sup>a</sup>
Thorleifsson et al (2009) [6]	Iceland, Denmark	European	Population based	3876	28031	Iceland: 33.3	Iceland: 57.2 (18.0)	Iceland: 27.1(5.2)	rs12970134
						Denmark: 61.9	Denmark: 58.4 (10.3)	Denmark: 25.8 (4.2)	
Renström et al (2009) [11]	Sweden	European	Population based	1038	3885	Cases: 58.7	Cases: 53.8 (7.3)	Cases: 30.4 (4.7)	rs17782313

						Controls: 35.8	Controls: 52.6 (9.5)	Controls: 25.7 (4.0)	
						Denmark: 61.0	Denmark: 58.4 (10.3)	Denmark: 25.8 (4.2)	
Wen et al (2010) [12]	China	East Asian	Case-control	1165	1136	Cases: 39.0	Cases: 60.3 (10.9)	Cases: 25.2 (3.4)	rs17782313
						Controls: 31.1	Controls: 59.1 (7.9)	Controls: 24.1 (3.0)	
Ng et al (2010) [13]	China	East Asian	Case-control	6013	1692	Cases: 45.6	Cases: 56.8 (13.3)	Cases: 25.1 (3.9)	rs12970134
						Controls 1: 45.5	Controls1: 15.4 (1.9)	Controls 1: 19.9 (3.5)	
						Controls 2: 45.5	Controls2: 41.2 (10.5)	Controls 2: 22.9 (3.3)	
Huang et al (2011) [14]	China	East Asian	Case-control	591	1200	50.0	50-70 (age range)	Not reported	rs17782313
Takeuchi et al (2011) [15]	Japan	East Asian	Case-control	6781	7307	Cases: 62.8	Cases: 63.4 (10.4)	Cases: 24.2 (3.8)	rs12970134

						Controls: 49.9	Controls: 65.2 (7.2)	Controls: 22.8 (2.9)	
Janipalli et al (2012) [16]	Indian	South Asian	Case-control	1712	1392	Cases: 56.2	Cases: 46.6 (9.3)	Cases: 26.1 (4.2)	rs17782313 <sup>a</sup>
						Controls: 52.8	Controls: 31.9 (5.7)	Controls: 20.0 (3.1)	

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<sup>a</sup> The study contained data on both rs17782313 and rs12970134 polymorphisms, and only the rs17782313 polymorphism was selected  
 EPIC, the European Prospective Investigation into Cancer; CoLaus, the Caucasian population of Lausanne; MRC, Medical Research Council; YT2D, young-onset T2D;  
 EFSOCH, the Exeter Family Study of Childhood Health; WTCCC, the Wellcome Trust Case Control Consortium

## Figure legends

**Fig. 1** Flow chart of meta-analysis for exclusion/inclusion of individual articles (or studies).

<sup>a</sup> One article (Loos et al, 2008) contained nine studies/cohorts

**Fig. 2** Meta-analysis of the association between the rs17782313 (or its proxy rs12970134) polymorphism near the *MC4R* gene and type 2 diabetes risk **(a)** without and **(b)** with adjustment for BMI under an additive genetic model. The sizes of the grey boxes are proportional to the weight of each study in the meta-analysis



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