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The V103I polymorphism of the MC4R gene and obesity: population based studies and meta-analysis of 29 563 individuals

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Abstract

Background—Previous studies have suggested that a variant in the melanocortin-4 receptor (MC4R) gene is important in protecting against common obesity. Larger studies are needed, however, to confirm this relation.

Methods—We assessed the association between the V103I polymorphism in the MC4R gene and obesity in three UK population based cohort studies, totalling 8,304 individuals. We also did a meta-analysis of relevant studies, involving 10,975 cases and 18,588 controls, to place our findings in context.

Finding—In an analysis of all studies, individuals carrying the isoleucine allele had an 18% (95% CI 4–30%, $p=0.015$) lower risk of obesity compared with noncarriers. There was no heterogeneity among studies and no apparent publication bias.

Interpretation—This study confirms that the V103I polymorphism protects against human obesity at a population level. As such it provides proof of principle that specific gene variants may, at least in part, explain susceptibility and resistance to common forms of human obesity. A better understanding of the mechanisms underlying this association will help determine whether changes in MC4R activity have therapeutic potential.

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Contributors

EHY, MSS, NJW and IB devised the study. EHY obtained and analysed the data, and together with MSS and IB interpreted the results. EHY and MSS drafted the manuscript. SF, AH, JH and AS participated in data collection. All authors commented on earlier drafts and approved the final version of the manuscript.

Conflict of interest statement

The authors declare no conflicts of interest.

Introduction

The melanocortin-4 receptor (MC4R) is part of the central melanocortin system, which is known to regulate food intake and energy homeostasis. Disruption of the MC4R gene in mice and humans results in hyperphagia and obesity. Loss of function mutations in the MC4R are the commonest known form of monogenic obesity and are found in 4-5% of subjects with severe obesity of onset in childhood.^{1 2}

By contrast, the role of MC4R variants in common, polygenic obesity is uncertain. With a carrier frequency of around 2-4%, the V103I missense variant is the most common coding MC4R polymorphism. A recent pooled analysis based on 3,631 cases and 4,082 controls suggested that, compared to noncarriers, individuals with the I103 allele might have a 31% reduced risk of obesity; however, this association had only marginal statistical significance.³ Large scale studies are required to reliably confirm or refute gene-disease associations.^{4 5} We therefore assessed the association between the MC4R V103I polymorphism and obesity in a series of population based studies, comprising 1,053 cases and 7,251 controls. These studies were included in a meta-analysis, providing total data on 10,975 cases and 18,588 controls.

Methods

Study populations

We used data from the Norfolk cohort of the European Prospective Investigation into Cancer (EPIC) and the MRC Ely Study. Ethics committees have approved both studies and all participants gave informed consent. EPIC is an ongoing prospective cohort study of chronic diseases comprising approximately 25,000 Norfolk residents aged 45-75 who were recruited from general practice registers between 1993 and 1997.⁶ It is an ethnically homogeneous Caucasian population. These participants completed a baseline health examination. From January 1998, we invited the cohort for a second health examination and 15,786 people had attended by October 2000. Details of recruitment, anthropometric measurements, health examinations and questionnaires following standardised protocols have been published.⁶ DNA was extracted from the 15,786 whole blood/EDTA samples (Whatman Biosciences, Ely, UK) taken at the second health examination.

For the purposes of this analysis, we examined data from two subcohorts of the 15,786 EPIC study participants who attended the second health examination. EPIC1 is a random sample of 5,000 participants who were free of baseline disease (cancer, coronary heart disease and diabetes), and that had fully arrayed DNA available, completed food frequency questionnaire data, and blood HbA1c and BMI measured at the two clinical assessments. EPIC2 comprises 3,345 participants with fully arrayed DNA available for genotyping. We excluded 692 participants from EPIC2 as they were also present in the EPIC1 sample set. However, we used this duplicate set to assess the concordance of our genotype results.

We also used data from the MRC Ely Study, a prospective population-based cohort study of the aetiology and pathogenesis of type 2 diabetes and related metabolic disorders.^{7 8} Again, the study population consists of an ethnically homogeneous Caucasian population in which phenotypic data have been recorded at clinical assessments using standardised protocols for anthropometric measurements. All participants were between 40 and 65 years of age at baseline. This cohort was recruited from a population-sampling frame with a high response rate (74%), making it representative of the general population for this area of eastern England. For the purposes of this analysis, we used data collected at the second health check, approximately four-and-a-half years from baseline.

The participants in each cohort were defined as obese cases and nonobese controls according to a baseline BMI of at least 30 kg/m² or BMI less than 30 kg/m², respectively.

Genotyping

We genotyped the EPIC1, EPIC2 and Ely study sets for the G→A (valine to isoleucine) substitution at codon 103 of the MC4R gene (rs2229616), obtained with TaqMan chemistry (Applied Biosystems, Warrington, UK). The percentage of each cohort successfully genotyped was 98.0%, 86.5% and 97.3% respectively for EPIC1, EPIC2 and Ely.

Statistical analysis

We tested for Hardy-Weinberg equilibrium using the χ^2 test. Based on previous reports we used a dominant genetic model, comparing common homozygotes (G/G) with carriers of the A allele (G/A or A/A). Stata version 8.0 was used for all analyses (Stata Corporation, Texas, USA).

Systematic review and meta-analysis

Case-control and cohort studies published before June 2005 in which the MC4R gene V103I polymorphism had been related to BMI were identified by electronic searches of PubMed, scanning of relevant reference lists, and by contacting authors of studies for any unpublished or additional tabulated data. We used MeSH and free text terms relating to the melanocortin-4 receptor (eg, “receptor, melanocortin, type 4”, “melanocortin 4 receptor”, “MC4R”) in combination with obesity (eg, “obesity”, “obesity, morbid”, “body weight”, “body mass index”, “thinness”, “weight”, “overweight”) and with polymorphism (eg, “polymorphism, single nucleotide”, “genes”, “mutation”, “genotype”, “variant”).

We only included studies in which obesity case-control status by genotype was available. Information was collected on other prespecified study-level covariates to explore possible sources of heterogeneity: case-control definition; whether studies included adults, children or both; ethnicity; relatedness between cases and controls; population based or selected individuals. To calculate a pooled estimate of the relation between genotype and obesity we used fixed and random effects models. Heterogeneity among studies was assessed by the heterogeneity *Q* statistic. Funnel plots and the Egger test were used to assess evidence of possible publication bias.

Role of the funding source

No funding source had any role in study design; collection, analysis, or interpretation of data; or the writing of the report.

Results

Effect of the V103I polymorphism on BMI in three studies of British Caucasians

Full BMI and genotype data were available for 8,304 participants. The genotypic distributions in the control populations were in agreement with those expected under Hardy-Weinberg equilibrium ($p > 0.05$). In a subgroup of 692 samples, concordance between genotyping methods was 99.9%. Table 1 shows demographic and anthropometric characteristics of study participants by V103I genotype for the three studies. We found that the mean age of participants varied by genotype ($p = 0.025$) in the Ely study set; however, this observation was not evident in the other cohorts and is likely to be a chance finding. There was no association between V103I genotype and BMI. Similarly, we found no statistically significant association between genotype and obesity (table 2). Adjustment for

age did not materially alter the results. However, because of our limited sample size we then combined these results in a meta-analysis of all available data.

Meta-analysis

A total of 25 datasets, including three from the present study, with 30,300 individuals met the inclusion criteria for the meta-analysis (figure 1).^{2 3 9-23} However, we could only calculate an odds ratio for 22 datasets ($n=29,563$). This total included unpublished additional data provided by two groups (Farooqi *et al* and Hebebrand *et al*) which supersedes previous publications (see figure 1 footnotes for details). Of the 22 datasets, 21 represented Caucasian populations; one contained data from Black Americans.¹⁵ Amongst the control populations, the isoleucine allele frequency ranged between 0.5-3.4% (figure 1). Using a fixed effects model we found that overall the V103I genotype was inversely associated with obesity (odds ratio 0.82; 95% confidence interval 0.70-0.96; $p=0.015$). There was no heterogeneity among studies ($Q=13.99$ (21 df); $p=0.87$); consequently, results under a random effects model were identical. A funnel plot of the association between V103I and obesity plotted against sample size showed a symmetrical distribution ($p = 0.326$), suggesting there was no apparent publication bias.

Discussion

These data from 10,975 cases and 18,588 controls confirm that individuals carrying the isoleucine allele have a lower risk of obesity compared with noncarriers. However, whereas a previous pooled analysis reported a 31% risk reduction,³ our data based on nearly four times as many individuals show this reduced risk may be around 18%, suggesting the original association was overestimated. Our study reinforces the need for large scale studies to reliably assess gene-disease associations.

Several studies have suggested that the V103I variant may be non-functional. Indeed, the V103I has been shown to possess a normal endogenous agonist ligand profile and normal receptor expression levels at the cell surface.^{2 3 10 24 25} However, recent functional studies have revealed that, compared to the wild-type receptor, the infrequent I103 allele is less responsive to agouti-related protein (AGRP).²⁶ AGRP is an endogenous antagonist of the MC4 receptor that stimulates energy intake and promotes weight gain.²⁷⁻³⁰ Thus the V103I-mediated attenuation in MC4R activation by AGRP might lead to a relatively weaker orexigenic signal; in turn, this may result in a comparatively lower risk of obesity in human populations. Collectively, these findings suggest that the V103I polymorphism may be causally associated with obesity risk. Alternatively, this variant may be in linkage disequilibrium with an unknown functional variant elsewhere in the MC4R gene or in regulatory regions.

Our analysis was potentially limited by a number of factors. We cannot assess the impact of unmeasured genetic or environmental modifiers on the size and direction of the association. However, there is no reported evidence of interdependency. Secondly, because of the infrequency of the V103I polymorphism and the magnitude of the association observed in the current study, we cannot exclude the possibility that this finding is a false positive; however, this explanation is unlikely given the size of our study and the role of this gene in monogenic obesity. Finally, differences in study designs and case definitions may also have distorted the magnitude of the association between the V103I genetic variant and obesity. Despite these differences, we found no statistical evidence of heterogeneity among studies.

In conclusion, in this meta-analysis of 29,563 individuals we confirm that the MC4R V103I genotype protects against common obesity. We estimate that 17% of obesity in the population is attributable to the common homozygous genotype. This polymorphism is the

first to be consistently associated with alterations in human obesity at the population level. As such, it provides proof of principle that specific genetic variants may, at least in part, explain susceptibility and resistance to common forms of human obesity. A better understanding of the mechanisms underlying this association will help determine whether changes in MC4R activity have therapeutic potential.

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† Received by personal correspondence with authors.

~ Data from the Swedish Obesity Study only.

* Includes additional data from the HERITAGE Family Study, unrelated parents only: a, Whites; b, Blacks.

‡ Data presented only for the Essen cohort from Geller, 2004; the Ausburg (KORA) cohort has been omitted and superseded by the KORA surveys published in Heid, 2005.

= Quebec Family Study: parent data only.

§ Supersedes earlier publications^{1, 31} and includes additional unpublished data (available from corresponding author on request).

∞ Result based on a re-analysis of raw data with inclusion of additional unpublished data (available from corresponding author on request) and supersedes earlier publications.^{24, 32-34}

Total excludes three studies with 0 carriers in one group and OR could not be calculated.^{11, 13, 17}

Figure 1. Meta-analysis of studies of MC4R V103I polymorphism and obesity

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Table 1
Demographic and anthropometric characteristics of study participants by MC4R V103I genotype

	Genotype		
	G/G	G/A or A/A	P _D value
EPIC1			
Number	4707 (96.2)	185 (3.8)	
Men	2090 (44.4)	80 (43.2)	0.90 [†]
Age (years)	57.2 (0.14)	56.3 (0.67)	0.22
BMI (kg/m²)	26.0 (0.05)	25.6 (0.26)	0.24
EPIC2			
Number	2551 (96.2)	102 (3.8)	
Men	1379 (54.1)	52 (51.0)	0.51 [†]
Age (years)	59.7 (0.17)	61.4 (0.83)	0.05
BMI (kg/m²)	26.2 (0.07)	26.4 (0.38)	0.41
Ely			
Number	732 (96.4)	27 (3.6)	
Men	303 (41.4)	15 (55.6)	0.14 [†]
Age (years)	54.0 (0.30)	50.6 (1.40)	0.03
BMI (kg/m²)	25.8 (0.16)	26.3 (0.70)	0.55

Data are numbers with percent in parentheses, or means with standard errors in parentheses.

BMI, body mass index; P_D, P-value for dominant genetic model (G/G versus A carriers).

[†] χ^2 test.

Table 2
Association of MC4R V103I genotype with obesity

	Number of individuals with V103I (%)		Unadjusted OR (95% CI, P value)	Adjusted OR (95% CI, P value)*
	Obese	Nonobese		
EPIC1	20/603 (3.3)	165/4 289 (3.8)	0.86 (0.53-1.37, p = 0.523)	0.87 (0.54-1.39, p = 0.554)
EPIC2	16/337 (4.7)	86/2 316 (3.7)	1.29 (0.75-2.23, p = 0.357)	1.29 (0.75-2.23, p = 0.363)
Ely	5/113 (4.4)	22/646 (3.4)	1.31 (0.49-3.54, p = 0.591)	1.52 (0.56-4.16, p = 0.411)

OR, odds ratio; CI, confidence interval.

* Adjusted for age.