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SHORT REPORT

First investigation of two obesity-related loci (*TMEM18*, *FTO*) concerning their association with educational level as well as income: the MONICA/KORA study

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What this paper adds´ box**Box 1: What is already known on this subject**

- There is strong evidence from genome-wide association studies that genetic variants are associated with BMI and risk of obesity. It is also known that low socioeconomic status is a risk factor for developing obesity.
- No study is published investigating the association between obesity-related genetic variants and socioeconomic status as well as whether socioeconomic factors mediate the genotype-BMI association.

Box 2: What this study adds

- The investigated two strongest obesity-related loci (TMEM18, FTO) showed no evidence for an association with educational level or income, which is an important finding for public discussions concerning prevention strategies of obesity. Public health interventions should focus not the genetic background, but lifestyle factors and living conditions.
- The genotype-BMI association was not modified by considering socioeconomic status.

ABSTRACT

Background: Strong evidence exists for an association between socioeconomic status and body mass index (BMI) as well as between genetic variants and BMI. The association of genetic variants with socioeconomic status was not investigated so far. The aim of our study was to investigate two obesity-related loci - the transmembrane 18 (*TMEM18*) and the fat mass and obesity associated (*FTO*) gene - for their association with educational level and per capita income, and to test whether the detected genotype-BMI association is mediated by these social factors. **Methods:** 12,425 adults from a large population-based study were genotyped for the polymorphism rs6548238 near *TMEM18* and rs9935401 within *FTO* gene. Data on educational level and per capita income were based on standardized questionnaires. **Results:** High educational level and high per capita income were significantly associated with decreased BMI (-1.503 kg/m^2 , $p < .0001$ / -0.820 kg/m^2 , $p < .0001$). Neither the polymorphism rs6548238 nor rs9935401 nor their combination were significantly associated with educational level ($p = 0.773$ / $p = 0.827$ / $p = 0.755$) or income ($p = 0.751$ / $p = 0.991$ / $p = 0.820$). Adjustment for social factors did not change the association between rs6548238 or rs9935401 and BMI. **Conclusions:** As far as we know, this is the first study investigating the association between polymorphisms and socioeconomic status. The polymorphisms rs6548238 and rs9935401 showed no association with educational level or income.

INTRODUCTION

It is without controversy that genetic, environmental and lifestyle factors contribute to the development of obesity [1-3] – a polygenic disorder with several genes involved.[4-9] The fat mass and obesity associated (*FTO*) gene has the strongest effect on body mass index (BMI) followed by the transmembrane 18 (*TMEM18*) gene.[4,6,7,10] Beside genetic variants, the socioeconomic status is a well established risk factor for BMI. Epidemiological studies repeatedly show that obesity is more prevalent in subjects of low educational level and income.[11-13] Furthermore, poor socioeconomic conditions in childhood lead to obesity risk in later life [14,15] and family socioeconomic status is inversely related to child obesity.[16] No study has yet looked at the questions whether there is an association between obesity-related genotypes and socioeconomic status and whether the socioeconomic status modulates the genotype-BMI association. As far as we know, our study is the first exploring these issues, for which we investigated polymorphisms of the two strongest obesity-related loci (*TMEM18*, *FTO*) in a large population-based sample of 12,425 subjects.

SUBJECTS AND METHODS

Study population

The World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project and the Cooperative Health Research in the Region of Augsburg (KORA) project conducted four independent cross-sectional population-based surveys (S1 to S4). For the present study, genotype data were available from 12,425 participants (6,251 men and 6,174 women) aged 25 to 74 years from the surveys S2, S3, and S4 (conducted 1989/1990, 1994/95 and 1999/2001). The study was approved by the ethics committee of the Bavarian

Medical Association. All participants gave written informed consent to genetic analysis. The potential of population stratification was small.[17] Details of the study population have been previously described.[18-20]

Body weight was measured in light clothing to the nearest 0.1 kg and height to the nearest 0.5 cm. BMI (kg/m^2) was calculated as body weight in kg divided by squared body height in m^2 . Educational level was categorized according to the highest level attained: primary (in Germany called "Volksschule, Hauptschule"), secondary ("Mittlere Reife, Realschule"), and tertiary ("Abitur, Fachhochschule, Universität") education. Dichotomization was done into low (primary) and high (secondary or tertiary) educational group. Per capita income was based on the total household net income divided by the number of household members. Households with eight or more persons were excluded ($N = 37$). For analyses, log-transformed per capita income was used.

Genotyping

Two single nucleotide polymorphisms (SNPs) were genotyped: rs6548238 C>T near *TMEM18* gene and rs9935401 G>A within *FTO* gene with minor allele frequencies (MAF) of 17.5 or 41.0 percent, respectively. SNP selection was based on a previous analysis by the same investigators in the same study population, where the minor alleles of rs6548238 and rs9935401 were significantly associated with BMI, and on literature reporting the strongest effects on BMI for these two loci.[6,7]

Samples were genotyped with the MassARRAY system using the iPLEX™ Gold chemistry (Sequenom, San Diego, CA, USA) and were analyzed in a matrix-assisted laser desorption ionisation time of flight mass spectrometer (MALDI TOF MS, Bruker Daltonik, Leipzig, Germany). 12.5 percent of samples were double-genotyped. Each SNP was tested for deviation from Hardy Weinberg equilibrium (HWE) by means of a

chi-square test. There was no violation of HWE ($p \geq 0.50$). Genotyping success rate represented 94.7 (rs9935401) and 94.6 (rs6548238) percent.

Statistics

Means (\pm standard deviation (s.d.)) or proportions for baseline characteristics of study population were computed. We explored a mediator-analysis according to surrogacy analyses [21], including the following criteria:[22] first, genotype associated with outcome BMI (model 1); second, mediator (educational level, income) associated with outcome (model 2); third, genotype associated with mediator (model 3), and fourth, including mediator as covariate into first model, genotype-outcome association abolishes (model 4). The association of genotypes and mediators (model 3) was performed by logistic (education) or linear regression (income), assuming an additive genetic model and adjusting for age, sex, and survey. The minor allele was always defined as the risk or effect allele. Income was log-transformed and quintiles were built. Moreover, we conducted gender-specific analyses. All statistical analyses were performed using the statistical package SAS Version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Study population

Mean age (\pm s.d.) was 49 (± 14) years and mean BMI was 26.97 (± 4.49) kg/m². 61 percent of the population attained primary school as the highest educational level. The median of per capita income was 1611.98 DM.

Association of genotypes with BMI (model 1 and 4)

There was a significant association between the polymorphisms rs6548238 and rs9935401 and BMI (model 1) (Figure 1). The combination of SNPs showed an estimate of 0.335 kg/m² ($p=1.11 \times 10^{-13}$) per risk allele. Adjustment for educational

level or log per capita income - as well as for both social factors together (model 4) - marginally changed beta estimates and p-values. Sex-specific analyses showed similar results. The proportion of BMI variance explained by the two SNPs was 0.005 percent.

Association of social factors with BMI (model 2)

Higher educational and income level were associated with decreasing BMI (Figure 1). Compared to the lowest quintile of per capita income, the effect size on BMI is gradually increasing from the second quintile with an estimate of -0.597 kg/m^2 to the fifth quintile with an estimate of -1.440 kg/m^2 . Similar results were observed for sex-specific analyses. Adjustment for log per capita income did not change the significance for the association between educational level and BMI. Adjustment for educational level changed the association between log per capita income and BMI in men, where statistical significance was lost. The proportion of BMI variance explained by the two social factors was 0.050 percent.

Association of genotypes with socioeconomic status

There was no significant association (model 3) between polymorphisms rs6548238 and rs9935401 or their combination and educational level or log per capita income (Figure 1). Sex-specific analyses showed similar results.

DISCUSSION

Our data replicate the result of an inverse association between educational level and BMI, both in men and women [23-25], but also gender-specific differences were reported.[11,13,26,27]

Concerning income, our analyses also showed a negative association with BMI in both genders. In the Cardiovascular Health Study, lower income was not associated with higher body weight in men, but in women.[28] This finding for women was

reported too in another study.[29] In other studies, a positive association between income level and BMI was reported for men.[11,13,25] Adjusting for educational level significantly changed the association between income and BMI in men, but adjustment for income hardly changed the association between educational level and BMI. This result indicates that for educational level the link is more direct than for income. One reason could be that for adults educational level remains rather stable, whereas income can change more rapidly.

Our major finding is the lack of an association between polymorphisms rs6548238 (*TMEM18*) or rs9935401 (*FTO*) and educational level or income. Furthermore, these social factors are no mediators in the genotype-BMI association.

Neither *TMEM18* nor *FTO* showed a significant association with educational or income level (Figure 1). Due to the fact that this is the first study investigating this association, our results cannot be directly compared with other studies.

There has already been some debate on the association between genetic predisposition on the one hand and social status and health inequalities on the other.[30,31] Furthermore, twin studies indicate a genetic contribution to health status. [32,33] The main objective for analysing the potential genetic contribution on health inequalities is the identification of target populations for prevention strategies.

It might be argued that there is little reason to believe that social status is associated with genotype. It is important, though, to verify this argument by empirical analyses.

Our results are limited by the fact that we have analyzed only two - but potentially important [6,7] - genetic loci (*TMEM18*, *FTO*). Future studies should include genome-wide association analyses.

In conclusion, our data provide some evidence for the association of genetic factors (*TMEM18*, *FTO*) with BMI. There is no evidence, that the polymorphisms are

associated with the socioeconomic factors investigated here as well as that the socioeconomic factors modulate the genotype-BMI association.

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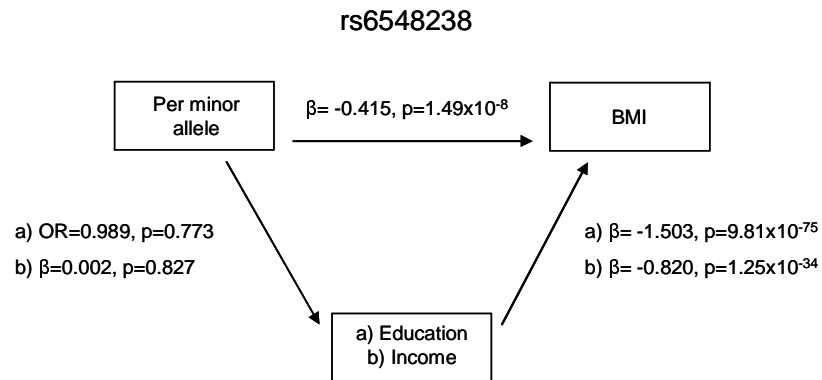
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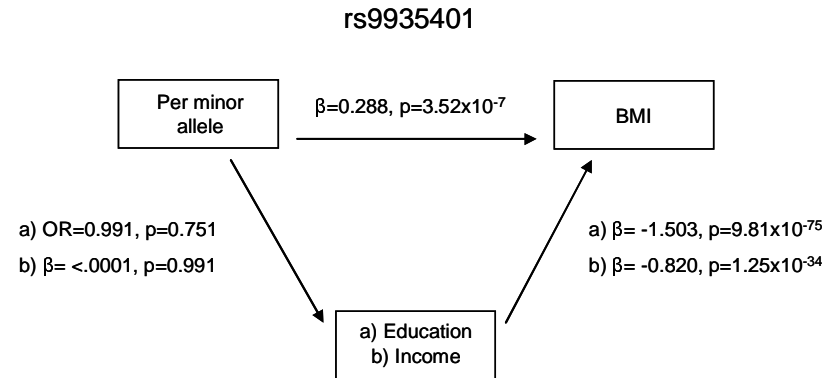
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Figure 1: Association between polymorphism (*genotype*), BMI (*outcome*) and educational level or income (*mediators*)

A)



B)



Beta estimates (β) / odds ratios (OR) and p-values are shown for the association between minor allele and BMI (model 1), mediators (educational level (low = ref.) (a) and income (b)) and BMI (model 2), and minor allele and mediators (model 3) for the whole study population; OR=0.989 corresponds to a β of -0.011 and OR=0.991 corresponds to a β of -0.009; results are shown separately for rs6548238 (A) and rs9935401 (B); all analyses were adjusted for age, sex, and survey; an additive genetic model was assumed; ref. = reference