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ORIGINAL ARTICLE

Replication of the association of common rs9939609 variant of *FTO* with increased BMI in an Australian adult twin population but no evidence for gene by environment (G × E) interaction

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Objective: To further investigate a common variant (rs9939609) in the fat mass- and obesity-associated gene (*FTO*), which recent genome-wide association studies have shown to be associated with body mass index (BMI) and obesity.
Design: We examined the effect of this *FTO* variant on BMI in 3353 Australian adult male and female twins.
Results: The minor A allele of rs9939609 was associated with an increased BMI ($P = 0.0007$). Each additional copy of the A allele was associated with a mean BMI increase of $\sim 1.04\,kg/m^2$ (~ 3.71 kg). Using variance components decomposition, we estimate that this single-nucleotide polymorphism accounts for $\sim 3\%$ of the genetic variance in BMI in our sample ($\sim 2\%$ of the total variance). By comparing intrapair variances of monozygotic twins of different genotypes we were able to perform a direct test of gene by environment (G × E) interaction in both sexes and gene by parity (G × P) interaction in women, but no evidence was found for either.
Conclusions: In addition to supporting earlier findings that the rs9939609 variant in the *FTO* gene is associated with an increased BMI, our results indicate that the associated genetic effect does not interact with environment or parity.
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Introduction

The prevalence of being overweight or obese has doubled in the last 30 years and has now reached epidemic proportions in western countries. In 2000, it was estimated that 67% of Australian adult men and 52% of Australian adult women were either overweight or obese.[1] Obesity causes or exacerbates many health problems including type 2 diabetes mellitus, cardiovascular disease, certain forms of cancer, respiratory complications and osteoarthritis.

Recently, three independent studies have shown that body mass index (BMI) is associated with variants in the fat mass- and obesity-associated gene, *FTO*. A genome-wide search for type 2 diabetes susceptibility genes in almost 39 000 participants identified a common variant (rs9939609) that is associated with an increased BMI in children and adults in a white European population.[2] In additional case–control studies, the association between this *FTO* single-nucleotide polymorphism (SNP) and type 2 diabetes was abolished by adjustment for BMI, suggesting that the association of this SNP with type 2 diabetes risk is mediated through BMI. After further population-based studies, it was concluded that homozygous carriers of the risk allele weighed on average 3 kg more than people lacking the allele with an increased odds ratio for obesity of 1.67.[2]

In addition to Frayling *et al.*,[2] another study[3] has also found the A allele of *FTO* variant, rs9939609, to be associated with body weight. Specifically, association was found between rs9939609 and several metabolic traits including obesity, waist circumference, fat mass and fasting serum levels in over 17 000 Danes. Analogous to Frayling *et al.*,[2] an association was initially found for type 2 diabetes and the

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results became nonsignificant when adjusting for BMI. In addition, a low physical activity was found to exacerbate the risk of increased BMI in homozygous A allele carriers compared with homozygous T allele carriers.[3]

Several other SNPs in the first intron of the *FTO* gene have also been associated with increased BMI. For example, Scuteri *et al*.[4] identified SNP rs9930506 (as well as a cluster of nearby SNPs that included rs9939609) as having a strong association with BMI, hip circumference and weight. Furthermore, Dina *et al*.[5] found a strong association between the SNP rs1121980 (also located in the first intronic region) and severe obesity (BMI $>40\,kg/m^2$). Although these multiple SNPs show evidences for association, both Scuteri *et al*.[4] and Dina *et al*.[5] conclude that they are not examples of multiple independently associated SNPs but rather they are in linkage disequilibrium with the same casual variant(s).

The *FTO* gene in humans is widely expressed in both fetal and adult tissues including adipose tissue.[2] The findings of higher subcutaneous fat mass in individuals carrying the rs9939609 risk allele[2] suggest that the *FTO* gene affects adipocyte function.[6] Here we investigate the relationship between rs9939609 and BMI in 3353 adults from 1955 twin families drawn from the Australian Twin Registry.

Methods

Participants and measures

Height and weight data were measured between 1992 and 1996 in the context of several clinical studies of adult twins and their families enroled on the Australian Twin Registry. The majority of participants were involved in more than one study and therefore most individuals had several measurements of BMI (calculated as weight (kg)/height (m^2)). Rules to determine which multiple measurement of BMI was used for each individual are specified elsewhere.[7] DNA was collected from some of these twins who participated in a 1992–1995 twin study based upon an Australian modified version (Mini-SSAGA-OZ) of the Semi-Structured Assessment for the Genetics of Alcoholism instrument (SSAGA; Bucholz *et al*.[8,9]). Participants gave written informed consent and provided blood samples from which DNA was isolated using standard protocols. Genetic studies were approved by the QIMR Human Research Ethics committee.

In total, the final sample included 3353 individuals (1144 men) from 1955 families and comprised 741 monozygotic (MZ) pairs, 657 dizygotic pairs and 557 singleton twins for whom both genotype and phenotype data were available. The participants were predominantly of European (mainly British Isles) ancestry (>95%) (that is, all four grandparents are of the same European origin) and aged 28–90 years (mean age was 44.6 ± 11.7 years) at the time of testing.

Genotyping

Forward and reverse PCR primers and an extension primer were designed using Sequenom MassARRAY Assay Design (version 3.0) software (Sequenom Inc., San Diego, CA, USA) and purchased from Bioneer Corporation (Daejeon, Korea). Genotyping was carried out in standard 384-well plates with 12.5 ng of genomic DNA used per sample. We used a modified iPLEX Gold Sequenom protocol in which half-reaction volumes were used in each of the PCR, SAP and iPLEX Gold stages giving a total reaction volume of 5.5 μl. The reaction products were desalted by diluting samples with 15 μl of water and 3 μl SpectroCLEAN resin (Sequenom) and were then spotted on a SpectroChip (Sequenom), processed and analysed on a Compact MALDI-TOF Mass Spectrometer by MassARRAY Workstation software (version 3.3) (Sequenom). Allele calls for each 384-well plate were reviewed using the cluster tool in the SpectroTyper software (Sequenom) to evaluate assay quality. Genotype error checking, including Mendelian inconsistencies and Hardy–Weinberg equilibrium (HWE) analyses, was performed using MERLIN[10] and PEDSTATS.[11]

Statistics

Preliminary analysis. Phenotypic data were screened for univariate outliers using SPSS 15.0 for Windows (SPSS Inc., 1989–2006). Those data with *z*-score values greater than ± 4.00 s.d. from the mean (only two individuals in the data set) were excluded from all reported analyses. A natural logarithmic transformation was performed on BMI to reduce the skewness of the distribution (hereafter called lnBMI and used in all further analyses). Thirty-seven individuals (nine men) were excluded from all reported analyses due to low DNA concentrations.

Gene by environment interaction ($G \times E$). As MZ twin pairs are genetically identical, any differences within pairs must be due to environmental influences. By performing an analysis of variance test on the homogeneity of the distributions of MZ within-pair variances (the mean of squared within-pair differences as described by Fisher[12]) for lnBMI for the three different genotypes (A/A, A/T and T/T), we can determine whether individuals with a certain genotype are more susceptible to environmental influences on lnBMI. If a genotype has a substantial effect on MZ within-pair variances, then we might expect the distribution of absolute pair differences to be heterogenous. The Levene F-test[13] (performed within SPSS) was used to verify the assumption of analysis of variance (that is, that variances across groups are equal).

Association analysis. Analysis of association between lnBMI and rs9939609 was performed using Quantitative Transmission Disequilibrium Test (QTDT),[14] which involves maximum-likelihood modelling of the raw data using a variance-component framework that allows for the simultaneous modelling of the means and variances. Analyses tested for population stratification (which can lead to spurious association) and locus dominance effects.

To test for population stratification, association effects are partitioned into orthogonal between- and within-family components. Between-family effects (β_B) reflect both genuine and spurious associations, whereas within-family (β_W) effects reflect only genuine association. Therefore, population stratification is indicated when $\beta_B \neq \beta_W$.[15,16] Analyses were run as described at http://www.sph.umich.edu/csg/abecasis/QTDT/. In earlier analyses using the same data,[7] the effects of age, age^2, age $\times$ birth and age^2 $\times$ birth were found to be significant. Therefore, these same covariates were included in the current analyses.

Results

Association analysis

A total of 3353 twin participants had both rs9939609 genotype data and phenotypes. The minor allele frequency observed in our sample was 0.390 (A allele) (minor allele frequencies were similar in both sexes at 0.385 and 0.393 in men and women, respectively). Analysis of all genotyped participants indicated a significant deviation from HWE ($P = 0.002$). However, analysis of related individuals can lead to bias in HWE testing (for example, Terwilliger[17]). A subsequent HWE analysis of unrelated individuals produced only a marginal deviation from HWE ($P = 0.0234$). Given the strong prior validation of the assay for rs9939609 and careful review of SpectroTyper software (Sequenom) allele clustering indicating high assay quality, we conclude that the deviation from HWE observed for this SNP occurred by chance (see for example, Hosking *et al.*[18]). As there was evidence for population stratification (at the 0.05 significance level; $\chi^2_1 = 7.79$, $P = 0.0053$), we proceeded with the within-family test of association as this guards against false-positive results due to population stratification.

The *FTO* A/T polymorphism, rs9939609, was found to be significantly associated with lnBMI ($\chi^2_1 = 11.57$, $P = 0.0007$). An increased BMI was associated with the A allele in an apparent additive fashion (no evidence for a non-additivity trend was found for men ($P = 0.386$) or women ($P = 0.219$) with an effect size of $\sim 1.04\,kg/m^2$ (equivalent to a mean weight increase of ~ 3.71 kg). Furthermore, the association signal was stronger in women ($1.39\,kg/m^2$) than in men ($0.67\,kg/m^2$). Table 1a shows adjusted means for BMI by sex and rs9939609 genotype. In addition, the differences in mean BMI within informative twin pairs (heterozygous dizygotic twins used in within-family association; *N* pairs = 263) are displayed in Table 1b separately for men, women and the sexes combined. The observed differences are in the expected direction and consistent with additivity (that is, AA > AT > TT). Most of the pair-wise comparisons hover around the conventional $\alpha = 0.05$ significance level, but the test of within-pair association using the combined sexes is highly significant (see Table 1b). In addition, the presence of at least one risk A allele increased the mean BMI by $0.98\,kg/m^2$ (as compared with the TT homozygotes; $P = 0.003$). The proportion of genetic variance in lnBMI due to rs9939609 was 2.98% (1.95% of the total variance). The specified covariates did not alter results, and there was no evidence of non-additivity (dominance or epistasis) or common environmental variance effects.

Table 1a Adjusted means[a] for BMI by sex and rs9939609 genotype (AA, AT and TT) for individuals with 95% CI for means in parentheses

	N	*AA*	N	*AT*	N	*TT*
Men	25	26.96 (25.74–28.17)	48	25.62 (24.61–26.62)	35	25.62 (24.59–26.65)
Women	38	27.13 (25.12–29.14)	96	25.33 (24.48–26.18)	68	24.35 (23.30–25.40)
Men and women[b]	105	26.74 (25.84–27.64)	241	25.42 (24.90–25.94)	180	24.65 (24.09–25.21)

Abbreviations: BMI, body mass index; CI, confidence interval; DZ, dizygotic. Note: means (95% CI) are observed across informative DZ sibpairs (*N* pairs = 263) included in within-family association. [a]Corrected for age, age^2, birth, age $\times$ birth, age^2 $\times$ birth as well as sex for men and women combined group only. [b]Men and women combined group also includes DZ opposite sex (DZOS) twin pairs.

Table 1b Maximum likelihood tests comparing mean BMI[a] between AA, AT and TT genotypes by sex

	Men			*Women*			*Men and women*[b]		
	N *pairs*	Δ *Mean*	P-*value*	N *pairs*	Δ *Mean*	P-*value*	N *pairs*	Δ *Mean*	P-value
AA vs AT	19	1.344	0.045	33	1.794	0.068	83	1.314	0.006
AT vs TT	29	0.002	0.997	63	0.982	0.068	158	0.770	0.019
AA vs TT	6	1.342	0.063	5	2.775	0.011	22	2.085	<0.001

Abbreviations: BMI, body mass index; DZ, dizygotic. [a]Corrected for age, age^2, birth, age $\times$ birth, age^2 $\times$ birth as well as sex for men and women combined group only. [b]Men and women combined group also includes DZ opposite sex (DZOS) twin pairs. Means are observed across informative DZ sibpairs (*N* pairs = 263) included in within-family association.

Tests of homogeneity of MZ within-pair differences between all three genotypes are displayed in Table 2 separately for men, women and the sexes combined. The Levene F-test was not significant (see Table 2), indicating that rs9939609 genotypes do not influence environmental variability in lnBMI in men, women and the sexes combined.

In an association study by Gutersohn *et al.*,[19] parity appeared to moderate the effects of the rs5443 variant of the guanine nucleotide-binding protein 3 (*GNβ3*) gene on female BMI. As parity information was available for the current data, we sort out to investigate if such an interaction existed between rs9939609 and female BMI. Means for female BMI by number of births and genotype are shown in Table 3. A nonsignificant Levene F-test was observed indicating that the *FTO* effect does not appear to have a stronger effect in parous (have given birth one or more times) or nulliparous (have never given birth) women,

Table 2 Tests of homogeneity of MZ within-pair differences

	N (pairs)	AA[a]	AT[a]	TT[a]	Levene statistic[b,c]	d.f.	P-value
Men	208	0.1804	0.2644	0.1346	1.071	2	0.345
Women	533	0.7645	1.2124	1.2816	0.228	2	0.796
Men and women	741[d]	0.6230	0.9784	0.9394	0.359	2	0.698

Abbreviation: MZ, monozygotic. Displayed are the within-pair variances of three genotypes (AA, AT and TT), Levene statistic and one-tailed probability (*P*-value) given for lnBMI by sex for MZ twin pairs. The within-pair variances of the MZ pairs are shown by genotypes in columns 3–5. If there were evidences of G × E, we would expect these variances to differ significantly. However, as shown in columns 6–8, there were no significant differences. [a]Variances multiplied by 1000. [b]Compares variances of AA to AT, AT to TT and AA to TT. [c]Levene statistic assumes equal variances across groups. [d]The final sample included 741 MZ pairs; therefore 741 MZ within-pair differences were tested.

Table 3 Means for BMI by number of children and rs9939609 genotype (AA, AT and TT) for women with 95% CI for means given in parentheses

Number of children[a]	N	AA	N	AT	N	TT
0–2	156	24.69 (23.88–25.49)	430	25.17 (24.75–25.60)	349	24.92 (24.43–25.72)
3+	103	26.16 (25.19–27.14)	355	25.59 (25.13–26.05)	286	25.67 (25.13–26.20)

Abbreviations: BMI, body mass index; CI, confidence interval. [a]Owing to small numbers, women with two births or less and three or more births were pooled into one category.

providing no evidence for gene by parity interaction (G × P) (data not shown).

Discussion

The association of the *FTO* SNP (rs9939609) with BMI has been found earlier in a white European population.[2] In adult population-based studies, the A allele of rs9939609 was associated with an increased BMI of $\sim 0.4\,kg/m^2$. Our analyses showed similar results, providing an independent replication of association between rs9939609 and BMI. In our sample, each additional copy of the rs9939609 A allele was associated with a mean BMI increase of $\sim 1.04\,kg/m^2$ that was equivalent to a mean weight increase of $\sim 3.71\,kg$. Furthermore, there was evidence of a stronger association of the variant in women than in men (effect size: 1.39 vs $0.67\,kg/m^2$). The reason for this finding may be a physiological or endocrinological gender effect(s). Sex differences in the genetic variation are expected due to male–female differences in fat distribution, deposition and accumulation in overall body composition. Recently, a study found an association between the *FTO* SNP and the female endocrinopathy, polycystic ovary syndrome, in more than 1700 women from the United Kingdom and 1000 women from Finland.[20] Analogous to the relationship between the *FTO* variant and the predisposition to type 2 diabetes,[2] it was semantically argued that the effect of *FTO* on polycystic ovary syndrome susceptibility is mediated through its effect on fat mass and in turn resulting in deleterious metabolic consequences. However, further investigation into possible gender effects is warranted and is planned for future research.

As an evidence for population stratification was found, we performed additional analyses to investigate potential causes of this finding. Using self-reported ancestral information, we defined sub-samples with (a) all four grandparents of European origin ($N = 1884$) and (b) more stringently, all four grandparents of British Isles origin (England, Scotland, Wales and Ireland) ($N = 1399$). However, evidence for population stratification remained significant within the European sub-group ($\chi^2_1 = 6.96$, $P = 0.0083$) and even remained when we made the further restriction to the British Isles group ($\chi^2_1 = 5.37$, $P = 0.0205$). This may reflect the significant stratification on the British population reported in the Wellcome Trust Case Control Consortium,[21] or inaccuracies in our self-report ancestry measures may introduce biases of unknown effect.

Owing to the nature of the sample, we were able to check for genotype by environment interaction by testing the homogeneity of MZ within-pair variances for the three different genotypes. Genotype by environment interaction refers to the possibility that individuals of different genotypes may respond differently to environments.[22] That is, do individuals of a certain genotype gain more weight than others of a different genotype when exposed to a given environment? Our results, however, did not indicate that rs9939609 genotypes influenced general environmental variability in lnBMI (as indicated by the nonsignificant Levene F-statistic in Table 2). Furthermore, substantial data were available on the number of births for women, thus enabling us to test how this may reduce or accentuate the effect of rs9939609 on BMI. However, number of births did not significantly alter the effect of this particular *FTO* genotype.

In contrast to the numerous studies finding significant association in white Europeans, rs9939609 does not appear to be associated with obesity in several other ethnic populations.[23,24] In four oceanic populations (two Melanesian (Munda and Paradise), one Micronesian (Rawaki) and one Polynesian (Tongan)), no significant association between the rs9939609 A allele and BMI or weight was found in the individual populations or when the participants were pooled,[24] although the sample sizes of this study were much smaller ($N = 320$) than those of earlier studies for European populations.[2,5] Furthermore, no association was found between several obesity phenotypes (including BMI, waist circumference and body fat percentage) and three *FTO* variants, including rs9939609, in over 3000 unrelated Han Chinese individuals in a population-based study[23] despite authors claiming there was sufficient power. These findings suggest that the contribution of this *FTO* polymorphism to predisposition to obesity is small or absent in oceanic and Han Chinese populations. Failure to find any association in

these populations may suggest that the effects of rs9939609 may be confined to those of European origin, or that there may be rarer, population-specific variants more strongly associated with BMI in these populations, given that the rs9939609-A allele frequencies were less in the oceanic (Munda: 0.295; Paradise: 0.193; Rawaki: 0.047; Tongan: 0.176) and Han Chinese (HCB (HapMap): 0.122) populations than in those of European origin (CEU (HapMap): 0.450; our sample: 0.390).

As a consequence, a further detailed association analysis of *FTO* variants in diverse populations is beneficial to fully elucidate the relationship between rs9939609 and BMI. Understanding how variation in the *FTO* gene region is associated with adiposity may provide insights into novel pathways involved in the control of obesity.

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