BRIEF REPORT

FTO Variants Are Associated With Obesity in the Chinese and Malay Populations in Singapore

Jonathan T. Tan,1 Rajkumar Dorajoo,2 Mark Seielstad,2 Xue Ling Sim,1 Rick Twee-Hee Ong,2 Kee Seng Chia,1 Tien Yin Wong,3,4 Seang Mei Saw,3,5 Suok Kai Chew,6 Tin Aung,3 and E-Shyong Tai1,7

OBJECTIVE—Association between genetic variants at the FTO locus and obesity has been consistently observed in populations of European ancestry and inconsistently in non-Europeans. The aim of this study was to examine the effects of FTO variants on obesity and type 2 diabetes in Southeast Asian populations.

RESEARCH DESIGN AND METHODS—We examined associations between nine previously reported FTO single nucleotide polymorphisms (SNPs) with obesity, type 2 diabetes, and related traits in 4,298 participants (2,919 Chinese, 785 Malays, and 594 Asian Indians) from the 1998 Singapore National Health Survey (NHS98) and 2,996 Malays from the Singapore Malay Eye Study (SiMES).

RESULTS—All nine SNPs exhibited strong linkage disequilibrium (r^2 = 0.6–0.99), and minor alleles were associated with obesity in the same direction as previous studies with effect sizes ranging from 0.42 to 0.68 kg/m^2 (P < 0.0001) in NHS98 Chinese, 0.65 to 0.91 kg/m^2 (P < 0.02) in NHS98 Malays, and 0.52 to 0.64 kg/m^2 (P < 0.0001) in SiMES Malays after adjustment for age, sex, smoking, alcohol consumption, and exercise. The variants were also associated with type 2 diabetes, though not after adjustment for BMI (with the exception of the SiMES Malays: odds ratio 1.17–1.22; P ≤ 0.026).

CONCLUSIONS—FTO variants common among European populations are associated with obesity in ethnic Chinese and Malays in Singapore. Our data do not support the hypothesis that differences in allele frequency or genetic architecture underlie the lack of association observed in some populations of Asian ancestry. Examination of gene-environment interactions involving variants at this locus may provide further insights into the role of FTO in the pathogenesis of human obesity and diabetes.

Diabetes 57:2851–2857, 2008

A recent genome-wide association study for type 2 diabetes using a U.K.-based population revealed a novel locus associated with BMI: the fat mass– and obesity-related gene (FTO) on chromosome 16 (1). The representative single-nucleotide polymorphism (SNP), rs9939609, was confirmed to be associated with elevated BMI after replication in more than 38,000 study participants of European ancestry. Further replication of this association has been observed in several populations of distinctly European ancestry (2–6). However, this association is inconsistent in populations of non-European ancestry. A study in Japanese showed an association between variants at this locus and obesity (7) that was not observed in African Americans (6) or Han Chinese (8). The aims of this study were 1) to determine the associations between previously identified obesity-associated SNPs at the FTO locus with obesity and type 2 diabetes in Chinese, Malays, and Asian-Indians and 2) to examine whether any associations were modulated by exercise.

RESEARCH DESIGN AND METHODS

This study utilized data from two cross-sectional studies: the 1998 Singapore National Health Survey (NHS98) (4,723 subjects) and the Singapore Malay Eye Study (SiMES) (3,280 subjects). NHS98 is a population-based, cross-sectional study of Chinese, Malays, and Asian Indians, aged between 18 and 69 years, that has previously been described (9,10). An interviewer-administered questionnaire was used to capture data on sociodemographic factors, smoking, and alcohol consumption. The level of physical activity was categorized into three groups: those who regularly exercised, defined as participation in any form of sports for at least 20 min for 3 or more days per week; those who occasionally exercised (<3 days per week); and those who did not exercise. BMI and blood pressure were measured for all subjects. Waist circumferences were measured at the narrowest part of the body below the costal margin, and hip circumference was measured at the widest part of the body below the waist. Fasting blood samples were drawn for measurement of serum lipids, glucose, and insulin after a 10-h overnight fast. Type 2 diabetes was defined as fasting glucose ≥7.0 mmol/l, 2 h postchallenge glucose (2HPG) ≥11.1 mmol/l, or self-reported type 2 diabetes. Impaired fasting glucose/impaired glucose tolerance was diagnosed if 6.0 mmol/l < fasting glucose ≤7.0 mmol/l or 7.8 mmol/l < 2HPG ≤11.1 mmol/l.

SiMES is a population-based, cross-sectional epidemiological study of Malay adults, aged between 40 and 79 years, that has previously been described (11–14). Serum lipids and glucose were measured in nonfasting venous samples. Type 2 diabetes was defined as random glucose ≥11.1 mmol/l or self-reported type 2 diabetes (additional information regarding the methods of NHS98 and SiMES can be found in an online appendix, available at http://dx.doi.org/10.2337/db08-0214).

Genotyping. Genotype data were available for 4,288 NHS98 subjects, comprising 2,919 Chinese (1,331 male and 1,588 female), 785 Malays (377 male and 408 female), and 594 Asian Indians (284 male and 310 female). In SiMES, genotype data were available for 2,996 subjects (1,442 male and 1,554 female).

10 FTO SNPs that have previously been described (1–6,8) were selected for this study (rs9009609, rs8050136, rs1421085, rs17817499, rs7193144, rs121980, rs9041028, rs9389073, rs9926289, and rs9930506). However, rs9930506 failed assay design and was not genotyped.
ASSOCIATION OF FTO VARIANTS AND OBESITY

Table 1: Clinical characteristics of the NHS98 and SiMES study populations

|                      | NHS 98 | NHS 98 SiMES | Indian | Indian SiMES | Malay | Malay SiMES |
|----------------------|--------|--------------|--------|--------------|-------|-------------|
| n                    | 2,919  | 785          | 594    | 2,996        | 48.1  | NA          |
| Male (%)             | 45.6   | 47.9         | 47.8   | 48.1         | NA    | NA          |
| Age (years)          | 37.9± 12.2 | 38.9± 12.5   | 40.6± 11.9 | 58.6± 11.0  | NA    | NA          |
| BMI (kg/m²)          | 22.7± 3.71 | 25.5± 4.96   | 25.1± 4.60 | 26.3± 5.11  | NA    | NA          |
| Waist-to-hip ratio   | 0.82± 0.07 | 0.83± 0.07   | 0.85± 0.07 | NA           | NA    | NA          |
| Waist circumference (cm) | 78.1±10.6 | 82.6±11.9   | 85.1±11.5 | NA           | NA    | NA          |
| HDL cholesterol (mmol/l) | 1.42±0.37 | 1.30±0.33   | 1.14±0.30 | 1.35±0.33   | NA    | NA          |
| LDL cholesterol (mmol/l) | 3.38±0.95 | 3.86±1.08   | 3.69±1.03 | 3.54±1.00   | NA    | NA          |
| Triglycerides (mmol/l) | 1.40±1.19 | 1.67±1.28   | 1.68±1.36 | 1.60±1.32   | NA    | NA          |
| Total cholesterol (mmol/l) | 5.41±1.04 | 5.81±1.15   | 5.51±1.10 | 5.62±1.16   | NA    | NA          |
| Fasting plasma glucose (mmol/l) | 5.62±1.30 | 6.09±2.23  | 6.23±2.17 | NA           | NA    | NA          |
| 2HPG (mmol/l)        | 6.65±2.76 | 7.37±3.55   | 7.63±4.07 | NA           | NA    | NA          |
| Systolic blood pressure (mmHg) | 120.±16.3 | 124.±19.3 | 121.±17.1 | 147.±23.7   | NA    | NA          |
| Diastolic blood pressure (mmHg) | 73.7±11.2 | 76.±12.0   | 73.6±12.0 | 79.7±11.2   | NA    | NA          |
| Hypertension         | 18.6    | 25.9         | 20.2    | 68.5         | NA    | NA          |
| Glucose tolerance (%)| 2,179 (74.7) | 473 (60.2)  | 362 (60.9) | 2,288 (76.4)* | NA    | NA          |
| IFG/IGT              | 515 (17.6) | 201 (25.6)  | 118 (19.8) | NA           | NA    | NA          |
| Type 2 diabetes      | 224 (7.7) | 111 (14.1)  | 114 (19.2) | 708 (23.6)  | NA    | NA          |
| Currently smoking (%)| 12.4    | 22.9         | 14.6    | 20.2         | NA    | NA          |
| Regularly exercise (%)| 4.7    | 17.6         | 22.8    | NA           | NA    | NA          |
| Consume alcohol (%)‡ | 45.1    | 7.3          | 33.3    | 1.6          | NA    | NA          |

Data are means ± SD or n (%) unless otherwise indicated. *SiMES participants with no diabetes; †regular exercise defined as participation in any form of sports for at least 20 min for 3 or more days per week; ‡individuals who consume at least 1 alcoholic beverage per month. IFG/IGT, impaired fasting glucose/impaired glucose tolerance; NA, not applicable.

RESULTS

Table 1 shows the clinical characteristics of the two study populations. Allele frequencies for the nine genotyped SNPs and test for HWE deviation are listed in online appendix Table 1. The MAFs for all nine SNPs were higher in Asian Indians (0.33–0.43) than in Malays (0.28–0.33) or Chinese (0.12–0.18). None of the SNPs showed significant deviation from HWE. Figure 1 illustrates the linkage disequilibrium between the nine FTO SNPs in the different ethnic populations. A high degree of linkage disequilibrium was observed between the SNPs, with similar patterns in all three ethnic groups in our population. In addition, the linkage disequilibrium structure of our population showed similarity to that of the European population (CEU population of HapMap [online appendix Fig. 1]).

Table 2 shows associations between the nine SNPs with obesity, impaired fasting glucose/impaired glucose tolerance, and type 2 diabetes. All nine FTO SNPs were associated with increased BMI with an effect size, per risk allele, of 0.42–0.68 kg/m² (P < 0.0001) in NHS98 Chinese, 0.65–0.91 kg/m² (P < 0.02) in NHS98 Malays, and 0.52–0.64 kg/m² (P < 0.0001) in SiMES Malays. FTO variants were also associated with an increased risk of type 2 diabetes in the NHS98 Chinese (odds ratio 1.32–1.42; P = 0.049), NHS98 Malays (1.52–1.63; P = 0.028) and SiMES Malays (1.20–1.24; P = 0.007). However, these associations were abolished after adjustment for BMI, except in the SiMES Malays (1.17–1.22; P = 0.026). No statistically significant associations were observed in Asian Indians.

We next examined the association between FTO SNPs with obesity-related traits. Table 3 summarizes the association between rs9939609 and these traits. We chose rs9939609 as the representative SNP in our study because it was the index SNP in the original study (1) and had one
of the strongest associations with BMI. In our study, rs9939609 also showed highly significant association with waist circumference in both NHS98 Chinese (P < 0.0001) and NHS98 Malay (P = 0.001); waist circumference data were not available for SiMES Malays. Borderline association was also observed with LDL cholesterol and triglyceride, the latter only after adjustment for BMI, in NHS98 Chinese samples. Details of the associations for the other SNPs are listed in online appendix Table 2. Meta-analysis of the association between this SNP and BMI for all four populations in our study was also performed. No significant heterogeneity was observed between the four populations in our study. Furthermore, meta-analysis showed no heterogeneity of effect between populations. We also examined the association between these SNPs and other obesity-related traits. Other than a strong association with waist circumference, only borderline associations were observed with LDL cholesterol and triglycerides. A recent study by Freathy et al. (17) showed associations with LDL cholesterol in the same direction as that observed in our study. Their study also suggested that much larger sample sizes than are currently available are required to detect the effect of these genetic variants on secondary traits related to obesity. Given the multiple associations tested, we also cannot exclude the possibility that these could represent false-positive findings.

RESULTS
In our study, FTO variants showed associations with obesity and type 2 diabetes in Chinese and Malays living in Singapore. Similar effects were not observed in Asian Indian samples from the NHS98 cohort. However, it should be noted that given the relatively small sample size (n = 594) for this ethnic group, we had only 40% power to detect changes in BMI of 0.5 kg/m² for this population. Furthermore, meta-analysis showed no heterogeneity of effect between populations. We also examined the association between these SNPs and other obesity-related traits. Other than a strong association with waist circumference, only borderline associations were observed with LDL cholesterol and triglycerides. A recent study by Freathy et al. (17) showed associations with LDL cholesterol in the same direction as that observed in our study. Their study also suggested that much larger sample sizes than are currently available are required to detect the effect of these genetic variants on secondary traits related to obesity. Given the multiple associations tested, we also cannot exclude the possibility that these could represent false-positive findings.

DISCUSSION
In our study, FTO variants showed associations with obesity and type 2 diabetes in Chinese and Malays living in Singapore. Similar effects were not observed in Asian Indian samples from the NHS98 cohort. However, it should be noted that given the relatively small sample size (n = 594) for this ethnic group, we had only 40% power to detect changes in BMI of 0.5 kg/m² for this population. Furthermore, meta-analysis showed no heterogeneity of effect between populations. We also examined the association between these SNPs and other obesity-related traits. Other than a strong association with waist circumference, only borderline associations were observed with LDL cholesterol and triglycerides. A recent study by Freathy et al. (17) showed associations with LDL cholesterol in the same direction as that observed in our study. Their study also suggested that much larger sample sizes than are currently available are required to detect the effect of these genetic variants on secondary traits related to obesity. Given the multiple associations tested, we also cannot exclude the possibility that these could represent false-positive findings.

RESULTS
In our study, FTO variants showed associations with obesity and type 2 diabetes in Chinese and Malays living in

DIABETES, VOL. 57, OCTOBER 2008

FIG. 1. Linkage disequilibrium (r²) between the nine FTO SNPs in the NHS98 and SiMES populations.
of negative selection against the of an evolutionary divergence that might reflect a history patterns of association such as these may occur as a result has been suggested that population differences in the loci between Europeans and Chinese may have contrib-
ted to the lack of association in other ethnic groups. It

FTO risk alleles in African

and Asian Indian (rs8050136 and rs9939609), both of which were strongly associated with obesity traits. Furthermore, comparisons of linkage disequilibrium patterns between our study populations and European (CEU) pop-

ulations from HapMap (excluding rs9926289, where no data were available based on NCBI Build36) revealed no major differences in this region. The nine SNPs tested were correspondingly in strong linkage disequilibrium with each other in our Chinese (r$^2$ = 0.60–0.99), Malay (r$^2$ = 0.77–0.99 in NHS98 and r$^2$ = 0.80–0.99 in SiMES), and Asian Indian (r$^2$ = 0.64–0.99) samples, as they were in the CEU population from HapMap (r$^2$ = 0.83–0.96 [online appendix Fig. 1]).

The common form of obesity is a multifactorial condi-
tion thought to develop from an intricate interplay of genes and environmental factors such as dietary habits and levels of physical activity. The occurrence of gene-
gene and gene-environment factors would, therefore, make it difficult to clearly elucidate the role of specific

| SNP     | rs9939973 | rs9940128 | rs1421085 | rs1121980 |
|---------|-----------|-----------|-----------|-----------|
| **NHS98 Chinese** (n = 2,919) | | | | |
| ΔBMI per risk allele present (kg/m$^2$) | 0.43 | 0.42 | 0.68 | 0.43 |
| $P^*$/P† | <0.0001/<0.0001 | 0.001/<0.0001 | <0.0001/<0.0001 | <0.0001/<0.0001 |
| **Glucose tolerance** | | | | |
| OR (95% CI)* for type 2 diabetes vs. NGT | 1.33 (1.01–1.74) | 1.32 (1.00–1.72) | 1.42 (1.04–1.93) | 1.19 (0.91–1.53) |
| $P^*$/P† | 0.036/0.132 | 0.043/0.15 | 0.024/0.128 | 0.187/0.434 |
| OR (95% CI) for IFG/IGT vs. NGT* | 1.10 (0.91–1.32) | 1.09 (0.90–1.31) | 1.15 (0.92–1.42) | 1.08 (0.90–1.29) |
| $P^*$/P† | 0.323/0.527 | 0.338/0.546 | 0.197/0.503 | 0.368/0.702 |
| **NHS98 Malay** (n = 785) | | | | |
| ΔBMI per risk allele present (kg/m$^2$) | 0.83 | 0.82 | 0.90 | 0.65 |
| $P^*$/P† | 0.001/0.002 | 0.002/0.002 | 0.001/0.001 | 0.011/0.015 |
| **Glucose tolerance** | | | | |
| OR (95% CI)* for type 2 diabetes vs. NGT | 1.61 (1.10–2.33) | 1.60 (1.09–2.32) | 1.59 (1.09–2.32) | 1.57 (1.08–2.25) |
| $P^*$/P† | 0.013/0.082 | 0.014/0.084 | 0.016/0.095 | 0.016/0.071 |
| OR (95% CI) for IFG/IGT vs. NGT* | 1.34 (1.03–1.74) | 1.35 (1.03–1.74) | 1.22 (0.93–1.58) | 1.37 (1.06–1.77) |
| $P^*$/P† | 0.028/0.075 | 0.025/0.067 | 0.144/0.331 | 0.015/0.033 |
| **NHS98 Asian-Indians** (n = 594) | | | | |
| ΔBMI per risk allele present (kg/m$^2$) | 0.24 | 0.23 | 0.03 | 0.28 |
| $P^*$/P† | 0.352/0.333 | 0.36/0.347 | 0.913/0.781 | 0.267/0.247 |
| **Glucose tolerance** | | | | |
| OR (95% CI)* for type 2 diabetes vs. NGT | 0.84 (0.59–1.19) | 0.85 (0.59–1.20) | 0.87 (0.60–1.25) | 0.94 (0.66–1.31) |
| $P^*$/P† | 0.341/0.356 | 0.349/0.365 | 0.467/0.564 | 0.711/0.74 |
| OR (95% CI) for IFG/IGT vs. NGT* | 0.95 (0.69–1.29) | 0.96 (0.70–1.30) | 0.90 (0.65–1.24) | 1.05 (0.77–1.41) |
| $P^*$/P† | 0.754/0.707 | 0.775/0.732 | 0.515/0.599 | 0.774/0.895 |
| **SiMES Malay** | | | | |
| ΔBMI per risk allele present (kg/m$^2$) | 0.55 | 0.55 | 0.64 | 0.52 |
| $P^*$/P† | <0.0001/<0.0001 | 0.001/<0.0001 | <0.0001/<0.0001 | <0.0001/<0.0001 |
| **Glucose tolerance** | | | | |
| OR (95% CI)* for type 2 diabetes vs. NGT | 1.23 (1.08–1.40) | 1.24 (1.08–1.40) | 1.20 (1.05–1.37) | 1.24 (1.08–1.40) |
| $P^*$/P† | 0.001/0.004 | 0.001/0.004 | 0.007/0.025 | 0.001/0.003 |

Continued on following page
genetic variants in obesity risk (19). Recent studies have already recognized the significance of environmental modulation in variants of \(LIPC\), \(APOA5\), and \(PPARG\) with metabolic traits (20). Likewise, possible explanations for the differences in associations seen in our population compared with the findings of Li et al. (8) could lie in different exposures to environmental or lifestyle factors between the populations. For example, Andreason et al. (4) reported that physical activity attenuated the effects of \(FTO\) variants on obesity. This may be relevant given that studies in Shanghai Chinese by Lee et al. (21) and Jurj et al. (22) have reported that an average of 35% of subjects participated in regular exercise compared with 14.7% of the NHS98 Singapore Chinese population. While our study found no significant interaction with physical activity, our study may have been underpowered to detect these interactions (assuming an MAF of 12%, we only had 40% power at an \(\alpha\) level of 0.05). Furthermore, recent findings related to the association between \(ROBO1\) variants and obesity have emphasized the importance of age-gene interactions that may result in nonreplication (23). The differences in average age between the two Chinese populations (37.9 \(\pm\) 12.2 years in NHS98 Chinese vs. 58.6 \(\pm\) 6.0 years in Han Chinese) may have contributed to the discrepancies. Although this is an interesting hypothesis, it should be noted that the \(FTO\) associations with BMI showed no heterogeneity across populations of European ancestry with greatly varying mean ages (1).

Interestingly, adjustment for BMI diminished but did not abolish the association with type 2 diabetes among SiMES Malays. Perhaps this indicates a direct effect of \(FTO\) with type 2 diabetes, which, to the best of our knowledge, has not been observed in other studies. Another possibility could relate to residual confounding by obesity. It is well known that compared with Caucasians of similar BMI, Asians have different levels of adiposity and, thus, risks of

### TABLE 2
Continued

| rs7193144 | rs17817449 | rs8050136 | rs9926289 | rs9939609 |
|-----------|------------|-----------|-----------|-----------|
| 0.63      | 0.67       | 0.68      | 0.68      | 0.66      |
| <0.0001/≤0.0001 | <0.0001/≤0.0001 | <0.0001/≤0.0001 | <0.0001/≤0.0001 | ≤0.0001/≤0.0001 |
| 1.42 (1.04–1.92) | 1.39 (1.01–1.90) | 1.40 (1.02–1.90) | 1.40 (1.02–1.90) | 1.37 (1.00–1.86) |
| 0.025/0.102 | 0.039/0.178 | 0.036/0.168 | 0.035/0.163 | 0.049/0.212 |
| 1.10 (0.89–1.37) | 1.14 (0.91–1.41) | 1.14 (0.91–1.40) | 1.14 (0.92–1.41) | 1.12 (0.89–1.38) |
| 0.366/0.729 | 0.241/0.578 | 0.25/0.611 | 0.223/0.568 | 0.313/0.684 |
| 0.82      | 0.91       | 0.86      | 0.88      | 0.89      |
| 0.002/0.002 | 0.001/0.001 | 0.001/0.002 | 0.001/0.001 | 0.001/0.001 |
| 1.52 (1.04–2.21) | 1.63 (1.11–2.38) | 1.53 (1.04–2.24) | 1.60 (1.09–2.32) | 1.57 (1.08–2.29) |
| 0.027/0.12 | 0.011/0.074 | 0.028/0.129 | 0.015/0.092 | 0.018/0.104 |
| 1.21 (0.93–1.57) | 1.25 (0.95–1.63) | 1.20 (0.91–1.56) | 1.24 (0.95–1.61) | 1.22 (0.93–1.59) |
| 0.154/0.331 | 0.103/0.243 | 0.186/0.392 | 0.113/0.267 | 0.136/0.318 |
| 0.12      | 0.10       | 0.04      | 0.11      | 0.10      |
| 0.658/0.458 | 0.715/0.527 | 0.877/0.719 | 0.674/0.487 | 0.70/0.532 |
| 0.93 (0.64–1.32) | 0.85 (0.58–1.23) | 0.87 (0.60–1.24) | 0.88 (0.61–1.27) | 0.96 (0.67–1.37) |
| 0.677/0.766 | 0.393/0.438 | 0.445/0.53 | 0.51/0.543 | 0.84/0.914 |
| 0.88 (0.63–1.21) | 0.85 (0.60–1.17) | 0.91 (0.66–1.25) | 0.87 (0.62–1.20) | 0.87 (0.63–1.20) |
| 0.432/0.404 | 0.327/0.294 | 0.576/0.565 | 0.411/0.378 | 0.419/0.369 |
| 0.62      | 0.64       | 0.63      | 0.61      | 0.64      |
| <0.0001/≤0.0001 | <0.0001/≤0.0001 | <0.0001/≤0.0001 | <0.0001/≤0.0001 | ≤0.0001/≤0.0001 |
| 1.21 (1.05–1.37) | 1.20 (1.05–1.37) | 1.20 (1.05–1.37) | 1.20 (1.05–1.37) | 1.21 (1.05–1.38) |
| 0.005/0.019 | 0.007/0.026 | 0.007/0.023 | 0.006/0.021 | 0.005/0.019 |

*Adjusted for age and sex; †adjusted for age, sex, current smoking, exercise (except in the SiMES population), BMI (for risk of type 2 diabetes), education, and alcohol consumption. NGT, normal glucose tolerance.
### TABLE 3

|                  | 1998 Singapore National Health Study (NHS98) | SiMES (SiMES) |
|------------------|---------------------------------------------|---------------|
|                  | Malay (n = 2,919)                           | Malay (n = 2,996) |
|                  | Asian Indians (n = 785)                     | SiMES Malay (n = 594) |
| **FTO SNPs**     |                                             |                |
| rs9939609        | 2,919                                       | 594            |
|                  | 1,10005                                     | 1,10005        |
| **VARIANTS AND OBESITY** |                                             |                |
| HDL cholesterol  | 1.42 ± 0.735 (mmol/l)                       | 1.42 ± 0.725 (mmol/l) |
| LDL cholesterol  | 3.36 ± 0.424 (mmol/l)                       | 3.44 ± 0.476 (mmol/l) |
| Triglycerides    | 1.18 ± 0.613 (mmol/l)                       | 1.05 ± 0.560 (mmol/l) |
| Waist (cm)       | 77.84 ± 7.40 (cm)                          | 79.09 ± 7.46 (cm) |
| Waist-to-hip ratio | 0.82 ± 0.038                              | 0.83 ± 0.038   |
| Systolic BP      | 73.6 ± 0.90 (mmHg)                         | 74.2 ± 0.90 (mmHg) |
| Diastolic BP     | 75.6 ± 0.83 (mmHg)                         | 76.4 ± 0.83 (mmHg) |
| **Genotypes**    |                                             |                |
| 0, 1, and 2      | 2,919                                       | 2,996          |
|                  | 1,10005                                     | 1,10005        |

Genotypes 0, 1, and 2 represent numbers of risk/minor alleles, which correspond with risk alleles in previous studies in Europeans. *Adjusted for age and sex; †adjusted for age, sex, tolerance; NA, not applicable; NGT, normal glucose tolerance.

type 2 diabetes (24). Consequently, adjusting for BMI may not fully account for the confounding effects of adiposity on the risk of type 2 diabetes in the SiMES Malays.

In conclusion, we have found that variants at the *FTO* locus are associated with obesity in ethnic Chinese and Malays living in Singapore. In addition, statistically significant associations with type 2 diabetes were observed in Chinese and Malays. These two ethnic groups represent a large proportion of the population living in Southeast Asia, a region wherein a dramatic increase in the burden of diabetes is anticipated over the next several decades (25). Our findings make it unlikely that differences in allele frequency or genetic architecture underlie the lack of association reported between these variants and obesity-related traits in Chinese Hans (8). However, it is still possible that varied linkage disequilibrium structures and lower MAFs could reduce power to detect associations in other populations. Given these findings, it seems important to explore interactions between these genetic variants with lifestyle factors (e.g., physical activity) to better elucidate possible gene-environmental interactions that may underlie population differences.

### REFERENCES

1. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry RJ, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Elliott SJ, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon L, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 316:889–894, 2007.

2. Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobsson P, Carlsson LM, Kess W, Vatin V, Cecouer C, Delplanque J, Vaillant E, Patton F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougnères P, Kovanis P, Marre M, Balkau B, Cauchi S, Chevre JC, Froogl P. Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nat Genet* 39:724–729, 2007.

3. Hinney A, Nguyen TT, Scharrer A, Steedel S, Bronner G, Muller TD, Gratert H, Ilig P, Wichmann HE, Rief W, Schaefer H, Hebebrand J. Genome-wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (*FTO*) variants. *PLoS ONE* 2:e1361, 2007.

4. Andreasen CH, Stender-Petersen KL, Mogensen MS, Torekov SS, Weigner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS, Clausen F, Sandbach A, Louritian T, Hansen L, Jorgensen T, Pedersen O, Hansen T. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes* 57:95–101, 2008.

5. Peeters A, Beckers S, Verrijken A, Roeven P, Peeters P, Van Gaal L, Van Hul W. Variants in the FTO gene are associated with common obesity in the Belgian population. *Hum Genet* 124:481–484, 2008.

6. Scuteri A, Sanna S, Chen WM, Uda M, Albus G, Straut J, Nagyir S, Nagaraja R, Usala M, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Elhert GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-wide association scan shows genetic variants in the FTO region are associated with obesity-related traits. *Am J Hum Genet* 81:1119–1129, 2007.

7. Onnini S, Tanaka Y, Takahashi H, Hasegawa K, Kashiwagi A, Kaku K, Kawamori R, Nakamura Y, Maeda S. Association of *FTO* gene variants with body fat accumulation. *Diabetes* 57:95–101, 2008.

8. Li H, Wu Y, Loos RJ, Hu FB, Liu Y, Wang J, Yu Z, Lin X. Variants in the fat mass–and obesity-associated (*FTO*) gene are not associated with obesity in a Chinese Han population. *Diabetes* 57:624–628, 2008.

9. Tai ES, Ordovas JM, Corella D, Deurenberg-Yap M, Chan E, Adiconis X, Chew SK, Loh LM, Tan CE. The TaqIB and -629C > G polymorphisms at the cholesteryl ester transfer protein locus: associations with lipid levels in a multiethnic population: the 1998 Singapore National Health Survey. *Clin Genet* 63:19–30, 2003.

10. Cutter J, Tan BY, Chew SK. Levels of cardiovascular disease risk factors in...
Singapore following a national intervention programme. *Bull World Health Organ* 79:908–915, 2001

11. Shankar A, Leng C, Chia KS, Koh D, Tai ES, Saw SM, Lim SC, Wong TY: Association between body mass index and chronic kidney disease in men and women: population-based study of Malay adults in Singapore. *Nephrol Dial Transplant* 23:1910–1918, 2008

12. Su DH, Wong TY, Wong WL, Saw SM, Tan DT, Shen SY, Loon SC, Foster PJ, Aung T: Diabetes, hyperglycemia, and central corneal thickness: the Singapore Malay Eye Study. *Ophthalmology* 115:964–968, 2008

13. Foong AW, Saw SM, Loo JL, Shen S, Loon SC, Rosman M, Aung T, Tan DT, Tai ES, Wong TY: Rationale and methodology for a population-based study of eye diseases in Malay people: the Singapore Malay eye study (SiMES). *Ophthalmic Epidemiol* 14:25–35, 2007

14. Wong TY, Chong EW, Wong WL, Loo JL, Shen S, Loon SC, Rosman M, Aung T, Tan DTH, Tai ES, Saw SM: Prevalence and causes of visual impairment and blindness in an urban Malay Population: the Singapore Malay Eye Study (SiMES). *Arch Ophthalmol* 126:1091–1099, 2008

15. Barrett JC, Fry B, Maller J, Daly MJ: Haploview: analysis and visualization of linkage disequilibrium and haplotype maps. *Bioinformatics* 21:263–265, 2005

16. Loos RJ, Bouchard C: *FTO*: the first gene contributing to common forms of human obesity. *Obes Rev* 9:246–250, 2008

17. Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, Ebrahim S, Shields B, Zeggini E, Weedon MN, Lindgren CM, Lang I, Melzer D, Carr A, Lawlor DA, Qin G, Smith GD, Mellström D, McCarthy MI, Ingelsson E, Hattersley AT, Weedon MN, Perry JR, Davey Smith G, Knight B, Gotley DC, Stoupis C, Delanty N, Larsson SC, Groop L, De Iuliis GN, MacRae CA, Morris AD, Elliott P, Jarvelin MR, Hattersley AT, Frayling TM: Common variation in the *FTO* gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. *Diabetes* 57:1419–1426, 2008

18. Helgason A, Palsson S, Thorleifsson G, Grant SF, Emilsson V, Gunnsdottir S, Adeyemo A, Chen Y, Chen G, Reynisdottir I, Benediktsson R, Hwin A, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Schafer H, Faruque M, Dowmatey A, Zhou J, Wilensky RL, Reilly MP, Rader DJ, Baggar Y, Christiansen C, Sigurdsson G, Hebebrand J, Pedersen O, Thorsteinsdottir U, Gulcher JR, Kong A, Rotimi C, Stefansson K: Refining the impact of TCF7L2 gene variants on type 2 diabetes and adaptive evolution. *Nat Genet* 39:218–225, 2007

19. Marti A, Moreno-Aliaga MJ, Hebebrand J, Martinez JA: Genes, lifestyles and obesity. *Int J Obes Relat Metab Disord* 28 (Suppl 3):S29–S36, 2004

20. Grarup N, Andersen G: Gene-environment interactions in the pathogenesis of type 2 diabetes and metabolism. *Curr Opin Clin Nutr Metab Care* 10:420–426, 2007

21. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P, Son HY: Epidemic obesity and type 2 diabetes in Asia. *Lancet* 368:1681–1688, 2006

22. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
Author/s:
Tan, JT; Dorajoo, R; Seielstad, M; Sim, XL; Ong, RT-H; Chia, KS; Wong, TY; Saw, SM; Chews, SK; Aung, T; Tai, E-S

Title:
FTO variants are associated with obesity in the Chinese and Malay populations in Singapore

Date:
2008-10-01

Citation:
Tan, J. T., Dorajoo, R., Seielstad, M., Sim, X. L., Ong, R. T. -H., Chia, K. S., Wong, T. Y., Saw, S. M., Chews, S. K., Aung, T. & Tai, E. -S. (2008). FTO variants are associated with obesity in the Chinese and Malay populations in Singapore. DIABETES, 57 (10), pp.2851-2857. https://doi.org/10.2337/db08-0214.

Persistent Link:
http://hdl.handle.net/11343/242752

File Description:
published version

License:
CC BY-NC-ND