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Genetic association of SNPs in the *FTO* gene and predisposition to obesity in Malaysian Malays

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Abstract

The common variants in the fat mass- and obesity-associated (*FTO*) gene have been previously found to be associated with obesity in various adult populations. The objective of the present study was to investigate whether the single nucleotide polymorphisms (SNPs) and linkage disequilibrium (LD) blocks in various regions of the *FTO* gene are associated with predisposition to obesity in Malaysian Malays. Thirty-one *FTO* SNPs were genotyped in 587 (158 obese and 429 non-obese) Malaysian Malay subjects. Obesity traits and lipid profiles were measured and single-marker association testing, LD testing, and haplotype association analysis were performed. LD analysis of the *FTO* SNPs revealed the presence of 57 regions with complete LD (D' = 1.0). In addition, we detected the association of rs17817288 with low-density lipoprotein cholesterol. The *FTO* gene may therefore be involved in lipid metabolism in Malaysian Malays. Two haplotype blocks were present in this region of the *FTO* gene, but no particular haplotype was found to be significantly associated with an increased risk of obesity in Malaysian Malays.

Key words: *FTO* gene; SNP; Obesity; Linkage disequilibrium; Haplotypes

Introduction

The World Health Organization (WHO) defines overweight as a body mass index (BMI) of >25 kg/m^2 and obesity as a BMI of >30 kg/m^2. The WHO has reported that, globally, overweight and obesity represent the fifth leading risk for death; furthermore, 44% of the diabetes burden, 23% of the ischemic heart disease burden, and between 7 and 41% of certain cancer burdens are related to overweight and obesity. Obesity is a complex disorder, with genetic and non-genetic factors playing crucial roles in an individual's predisposition to it. Many recent studies, including genome-wide association studies (GWAS), have reported that single nucleotide polymorphisms (SNPs) are associated with obesity-related traits in various populations (1-5).

FTO gene variants have been widely studied for their association with obesity. Frayling et al. (1) first discovered in a GWAS that the rs9939609 variant of *FTO*, with clusters of SNPs in the first intron, was strongly associated with BMI in the UK population. Following this finding, an association between *FTO* SNPs and obesity traits was detected in people of European ancestry (2), Sardinians (6), and African Americans (7), as well as in a Belgian cohort (8), East Asian population (9), Japanese population (10,11), a Sorbian population in Germany (12), a Chinese population in Beijing (13), in an Indian population (14), and many other populations. Compared with other *FTO* variants, rs9939609 showed the strongest effect on BMI in these studies.

FTO is expressed in the hypothalamus, a region that is crucial for the control of appetitive behavior (15,16). Animal studies have shown that *FTO* has an effect on energy homeostasis (17), but the true physiological role of *FTO* is yet to be explored (18). Although initial reports on *FTO* stated that the functions and pathways linked to the *FTO* gene are largely unknown (1), structural analysis of *FTO* has revealed that it belongs to members of the non-heme 2-oxoglutarate-dependent oxygenase superfamily, which are involved in post-translational modification, DNA repair, and fatty acid metabolism (19,20). Recent studies have suggested that *FTO* may play an important role in adipogenesis, lipogenesis, and mitochondrial function in skeletal muscle (21,22).

In the current study, our objective was to examine the effects of *FTO* SNPs on obesity-related traits and to study the linkage disequilibrium (LD) pattern and haplotype block in the Malaysian Malays. To accomplish this, we genotyped 31 SNPs on the *FTO* gene selected from previous studies and GWAS.

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Subjects and Methods

Subjects

The participants were 587 subjects from the Wellness Program of a public university in Kuala Lumpur, an annual voluntary health screening program for the staff, as well as from a community of the Bera district of Pahang, a State on the east coast of Peninsular Malaysia. All subjects reported that they belonged to the Malay ethnic group for at least three generations. In accordance with the WHO cutoffs for obesity, subjects with a BMI of 30 kg/m^2 were categorized as obese and those with a BMI below 30 kg/m^2 as non-obese. The Medical Ethics Committee (MEC Ref. No. 672.23) of the university Medical Center approved the study protocol and written informed consent was obtained from all participants.

Clinical measurements

Anthropometric measurements such as height, body weight, BMI, waist circumference, hip circumference, waist-to-hip ratio, systolic blood pressure, and diastolic blood pressure were recorded. After an overnight fast, 10 to 15 mL blood was collected from each subject for routine biochemical measurements. Total cholesterol, total triglyceride, high-density lipoprotein cholesterol, serum low-density lipoprotein cholesterol (LDL-C), and triglyceride levels were measured using standard clinical laboratory techniques.

DNA isolation from human buccal swabs

Buccal swabs were collected and genomic DNA was obtained by using the i-genomic CTB DNA extraction kit (iNtRON Biotechnology, Korea). This extraction procedure consists of six main steps: prelysis, lysis, precipitation, DNA binding, washing, and elution with buffers, proteinase K, and RNase A.

DNA measurement

The concentration and purity of DNA was measured using a Nanodrop spectrophotometer to determine absorbance at wavelengths of 260 and 280 nm and by agarose gel electrophoresis.

Sequenom MassARRAY® iPLEX Platform (MALDI-TOF)

Genotyping of 31 SNPs of the *FTO* gene was performed with the Sequenom MassARRAY platform (Sequenom, USA). The variants were selected from information provided by previous GWAS and association studies in various populations.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was determined in both cases and controls (23) and genotype and allelic frequencies were also determined in cases and controls. Prior to statistical analysis, BMI and triglyceride data were normalized by natural log transformation. The general linear method was used to adjust for age and gender when assessing the effects of SNPs on obesity parameters and lipid levels. The results of association analysis for the SNPs and obesity parameters indicated that the additive model best fitted the data. Data are reported as means ± SD. Bonferroni's adjustment was performed to correct for multiple tests on multiple markers ($\alpha = 0.05/30$). Statistical analysis was performed using the SPSS version 16 software.

LD block construction and haplotype analysis were performed with the Haploview software (version 4.2) to measure the LD coefficient (D'). A permutation test with 5000 replications was used to obtain empirical levels of significance. Adjustment for multiple testing was performed by obtaining P values from the permutation test with the Haploview software. The power of the study, calculated using the Quanto version 1.2.4 software, was 87%.

Results

Table 1 shows the characteristics of the 587 subjects who participated in the study. The allele frequencies of 30 SNPs in the *FTO* gene are summarized in Table 2. The *FTO*

Table 1. Characteristics of the subjects in this study.

Characteristics	Non-obese subjects	Obese subjects	Pooled subjects
Height (m)	1.59 ± 0.09 (N = 429)	1.57 ± 0.09 (N = 158)	1.58 ± 0.09 (N = 587)
Weight (kg)	63.25 ± 10.77 (N = 429)	83.32 ± 11.82 (N = 158)	68.65 ± 14.20 (N = 587)
BMI (kg/m^2)	24.92 ± 3.09 (N = 429)	33.83 ± 3.18 (N = 158)	27.32 ± 5.04 (N = 587)
WC (cm)	85.25 ± 10.22 (N = 429)	100.76 ± 8.57 (N = 158)	89.43 ± 11.97 (N = 587)
HC (cm)	98.17 ± 7.31 (N = 429)	113.18 ± 8.04 (N = 158)	102.21 ± 10.04 (N = 587)
WHR	0.87 ± 0.08 (N = 429)	0.89 ± 0.07 (N = 158)	0.87 ± 0.08 (N = 587)
SBP (mmHg)	128.55 ± 17.38 (N = 429)	137.04 ± 18.32 (N = 158)	130.84 ± 18.02 (N = 587)
DBP (mmHg)	80.46 ± 11.38 (N = 428)	87.35 ± 12.28 (N = 158)	82.32 ± 12.02 (N = 586)
TG (mM)	1.42 ± 0.93 (N = 302)	1.56 ± 0.67 (N = 107)	1.46 ± 0.86 (N = 409)
HDL-C (mM)	1.32 ± 0.28 (N = 302)	1.25 ± 0.25 (N = 107)	1.30 ± 0.27 (N = 409)
TC (mM)	5.49 ± 0.91 (N = 302)	5.43 ± 0.98 (N = 107)	5.47 ± 0.93 (N = 409)
LDL-C (mM)	3.53 ± 0.80 (N = 299)	3.46 ± 0.87 (N = 106)	3.51 ± 0.82 (N = 405)
Age (years)	48.16 ± 10.19 (N = 429)	48.66 ± 9.03 (N = 158)	48.29 ± 9.89 (N = 587)

Data are reported as means ± SD, with number of patients within parentheses. BMI = body mass index; WC = waist circumference; HC = hip circumference; WHR = waist-to-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol.

Table 2. Allelic distribution among obese and non-obese subjects.

Name	Chromosome position	MAF	Assoc. allele	Alleles	Frequencies (cases, controls)	χ^2 (d.f. = 1)	P	HWE (cases/controls)
rs1077128	53791653	0.336	G	G:T	0.668, 0.662	0.034	1.000	0.137/0.516
rs11643744	53791798	0.355	G	A:G	0.370, 0.350	0.428	1.000	0.785/0.759
rs7186521	53792922	0.32	A	A:G	0.684, 0.678	0.029	1.000	0.134/0.892
rs13334933	53795636	0.337	A	A:G	0.671, 0.660	0.13	1.000	0.212/0.563
rs16952517	53797057	0.27	A	G:A	0.304, 0.258	2.503	0.9198	0.538/0.522
rs6499643	53797518	0.226	T	T:C	0.804, 0.763	2.156	0.9694	0.970/0.420
rs4784323	53797565	0.129	G	G:A	0.873, 0.869	0.032	1.000	0.297/0.472
rs7206790	53797908	0.296	G	C:G	0.297, 0.295	0.007	1.000	0.394/0.944
rs9939973	53800568	0.34	A	G:A	0.345, 0.338	0.05	1.000	0.278/0.519
rs1421085	53800954	0.307	C	T:C	0.313, 0.304	0.09	1.000	0.210/0.451
rs1558902	53803574	0.307	A	T:A	0.313, 0.304	0.09	1.000	0.210/0.451
rs10852521	53804965	0.266	C	C:T	0.741, 0.732	0.087	1.000	0.343/0.839
rs16952522	53807498	0.156	G	C:G	0.171, 0.150	0.74	1.000	0.718/0.212
rs17817288	53807764	0.298	G	G:A	0.709, 0.699	0.101	1.000	0.558/0.856
rs1121980	53809247	0.342	T	C:T	0.345, 0.340	0.022	1.000	0.778/0.619
rs16945088	53812524	0.084	A	A:G	0.918, 0.915	0.024	1.000	0.996/0.493
rs17817449	53813367	0.307	G	T:G	0.316, 0.303	0.196	1.000	0.134/0.890
rs8050136	53816275	0.307	A	C:A	0.313, 0.304	0.09	1.000	0.210/0.766
rs9935401	53816838	0.308	A	G:A	0.316, 0.305	0.133	1.000	0.134/0.820
rs3751812	53818460	0.307	T	G:T	0.313, 0.304	0.09	1.000	0.210/0.766
rs9939609	53820527	0.307	A	T:A	0.316, 0.304	0.163	1.000	0.134/0.766
rs7190492	53828752	0.129	A	G:A	0.136, 0.126	0.214	1.000	0.165/0.598
rs7204609	53833605	0.338	C	T:C	0.348, 0.334	0.191	1.000	0.703/0.278
rs17218700	53844579	0.135	G	G:A	0.886, 0.857	1.709	0.986	0.462/0.748
rs11642841	53845487	0.145	C	C:A	0.864, 0.852	0.266	1.000	0.476/0.358
rs1861867	53848561	0.126	T	C:T	0.130, 0.125	0.053	1.000	0.352/0.303
rs11075994	53850079	0.127	G	G:A	0.899, 0.864	2.567	0.913	0.747/0.993
rs1421090	53850170	0.344	C	T:C	0.399, 0.324	5.713	0.331	0.217/0.514
rs17818902	53871806	0.245	T	T:G	0.756, 0.754	0.006	1.000	0.810/0.613
rs7191513	53990523	0.323	A	G:A	0.348, 0.314	1.263	0.997	0.074/0.793

MAF = minor allele frequency; d.f. = degrees of freedom; HWE = Hardy-Weinberg equilibrium. *P value was generated using 5000 permutated chi-squares.

rs1861869 SNP deviated from Hardy-Weinberg equilibrium (HWE case/control = 0.863/0.025) and was therefore not included in the analysis. After Bonferroni's correction and a permutation test with 5000 replications for the 30 SNPs, there was no significant difference in allelic frequency for any of the *FTO* SNPs between the obese and non-obese groups. Table 3 shows the genotype frequencies of all *FTO* SNPs. There was no significant difference in genotype frequency for any of the *FTO* SNPs between the obese and non-obese groups.

The results of testing the single-marker association of 30 *FTO* SNPs with obesity traits are summarized in Figure 1. After Bonferroni's adjustment was performed for multiple corrections, α was 0.016 (-log10 P = 2.70). The SNP rs17817288 was significantly associated with LDL-C (P = 0.001) in Malaysian Malays after adjustment for age and gender. None of other SNPs presented a significant association with obesity parameters.

Figure 2 shows the LD pattern of the *FTO* gene. D prime value (D') of 100% indicates the complete LD. D' values of 100% are not shown (the box is empty). The boxes in bright red are with D' values of 100%. The boxes with values of D' < 100% are in shades of pink or red. When we examined the LD of the *FTO* region, we found two haplotype blocks of 1 and 44 kb. The strongest LD was seen in the second block, which showed 48 regions with complete LD and 69 regions with high LD (D' = 80-99%).

There are 11 haplotypes in the region of the *FTO* gene. Table 4 shows the first and second blocks of the *FTO* haplotypes. The GA, AA, and AG haplotypes in block 1 showed

frequencies of 36, 33, and 32%, respectively. In block 2, the TTCCGCATCGGTGCGC, CACCGTAGAATAGTGA, CACGGTAGAATAGTGC, TTTCACATCGGTGTAC, TTTCACATCGGTATGC, and TTCCGCGTCGGTGTGC haplotypes had frequencies of 32, 14, 14, 13, 12, and 5%, respectively. The TTCCATGTCGGTGTGC and CACC GTAGAATAGTGC haplotypes had lower frequencies (<5%). There were no significant differences in haplotype frequencies between obese and non-obese subjects. After permutation test correction with 5000 permutations, none of the haplotypes was associated with obesity.

Discussion

There were no significant differences in allelic or genotype frequencies of the 30 *FTO* SNPs between the obese and non-obese groups in the Malaysian Malay population. Recent studies have pointed out that the SNPs in the *FTO* gene contribute to obesity and obesity-related traits in various populations around the globe (1,3,24-27). Single-marker analysis revealed that rs17817288 was significantly associated with LDL-C levels (P = 0.001) in Malaysian Malays. A recent study (22) showed that, as a transcriptional coactivator, *FTO* might play an important role in the transcriptional regulation of adipogenesis and suggested that *FTO* might be involved in the regulation of fat development and maintenance. Therefore, we speculated that the *FTO* rs17817288 SNP may have an effect on adipogenesis in Malaysian Malays, which is consistent with findings by Wu et al. (22) concerning the functional effects of the *FTO* gene. The *FTO* rs9939609 SNP was chosen as representative of *FTO* SNPs in the present study because this locus was highlighted in many studies as having the strongest effect on obesity; it was also the key signal identified in the GWAS (1). A meta-analysis reported that 21 of 29 studies have shown a significant association between obesity and rs9939609 (5). However, this SNP had no effect on obesity in the Malaysian Malay population.

A meta-analysis reported that the minor allele frequency (MAF) for rs9939609 varies across the global population. The MAF of the *FTO* rs9939609 polymorphism was lower (0.31) in the Malaysian Malay population compared to the previously reported range of 0.38 to 0.46 in European populations (1,8,28). For example, the MAF was 0.31 to 0.37 in Hispanics, 0.34 to 0.44 in Caucasians, 0.17 in South Americans, 0.36 in Africans, 0.11 to 0.20 in Asians, 0.25 in Singaporean Malays, 0.13 in Singaporean Chinese, and 0.42 in Singaporean Indians (5,29,30). In addition, the MAF for rs1421085, rs1558902, rs17817449, rs3751812, rs9939609, and rs8050136 was similar across these six SNPs. The MAF for the SNPs is 0.31.

We investigated the LD structure of the *FTO* SNPs in Malaysian Malays. Linkage analysis showed 57 regions with complete LD in the *FTO* gene. Our results showed that 15 of the 30 *FTO* SNPs (50%) are in high LD (D ≥ 0.88) with

Table 3. Genotype distribution among obese and non-obese subjects.

	Non-obese			Obese		
rs1077128	GG	GT	TT	GG	GT	TT
	43.12	46.15	10.72	47.47	38.61	13.92
rs10852521	CC	TC	TT	CC	TC	TT
	53.38	39.63	6.99	56.33	35.44	8.23
rs11075994	AA	AG	GG	AA	AG	GG
	1.86	23.54	74.59	1.27	17.72	81.01
rs1121980	CC	TC	TT	CC	TC	TT
	44.06	43.82	12.12	44.94	41.14	13.92
rs11642841	AA	CA	CC	AA	CA	CC
	1.63	26.34	72.03	2.53	22.15	75.32
rs11643744	AA	GA	GG	AA	GA	GG
	41.96	46.15	11.89	39.24	47.47	13.29
rs13334933	AA	AG	GG	AA	AG	GG
	42.89	46.15	10.96	47.47	39.24	13.29
rs1421085	CC	CT	TT	CC	CT	TT
	10.03	40.79	49.18	12.03	38.61	49.37
rs1421090	CC	CT	TT	CC	CT	TT
	11.19	42.42	46.39	18.35	43.04	38.61
rs1558902	AA	AT	TT	AA	AT	TT
	10.02	40.79	49.18	12.03	38.61	49.37
rs16945088	AA	AG	GG	AA	AG	GG
	83.45	16.08	0.47	84.18	15.19	0.63
rs16952517	AA	AG	GG	AA	AG	GG
	7.23	37.06	55.71	10.13	40.51	49.37
rs16952522	CC	GC	GG	CC	GC	GG
	72.96	24.01	3.03	68.35	29.11	2.53
rs17218700	AA	AG	GG	AA	AG	GG
	1.86	24.94	73.19	1.9	18.99	79.11
rs17817288	AA	AG	GG	AA	AG	GG
	8.86	42.42	48.72	9.49	39.24	51.27
rs1861867	GG	GT	TT	GG	GT	TT
	77.16	20.75	2.1	76.58	20.89	2.53
rs3751812	GG	GT	TT	GG	GT	TT
	48.72	41.72	9.56	49.37	38.61	12.03
rs4784323	AA	GA	GG	AA	GA	GG
	2.1	21.91	75.99	2.53	20.25	77.22
rs6499643	CC	TC	TT	CC	TC	TT
	4.9	37.53	57.58	3.8	31.65	64.56
rs7186521	AA	GA	GG	AA	GA	GG
	46.15	43.36	10.49	49.37	37.97	12.66
rs7190492	AA	AG	GG	AA	AG	GG
	1.86	21.45	76.69	3.16	20.89	75.95
rs7191513	AA	GA	GG	AA	GA	GG
	9.55	43.59	46.85	15.19	39.24	45.57
rs7204609	CC	TC	TT	CC	TC	TT
	12.35	42.19	45.45	12.66	44.3	43.04
rs7206790	CC	CG	GG	CC	CG	GG
	49.65	41.72	8.62	50.63	39.24	10.13
rs8050136	AA	CA	CC	AA	CA	CC
	9.56	41.72	48.72	12.03	38.61	49.37
rs9935401	AA	GA	GG	AA	GA	GG
	9.56	41.96	48.48	12.66	37.97	49.37
rs9939609	AA	AT	TT	AA	AT	TT
	9.56	41.72	48.72	12.66	37.97	49.37
rs9939973	AA	AG	GG	AA	AG	GG
	12.12	43.36	44.52	13.92	41.14	44.94
rs17817449	GG	GT	TT	GG	GT	TT
	9.32	41.96	48.72	12.66	37.97	49.37
rs17818902	GG	GT	TT	GG	GT	TT
	5.59	38	56.41	6.33	36.08	57.59

*P value was generated using the chi-square test. There was no significant difference in genotype frequency of each of the SNP between the obese and non-obese subjects.

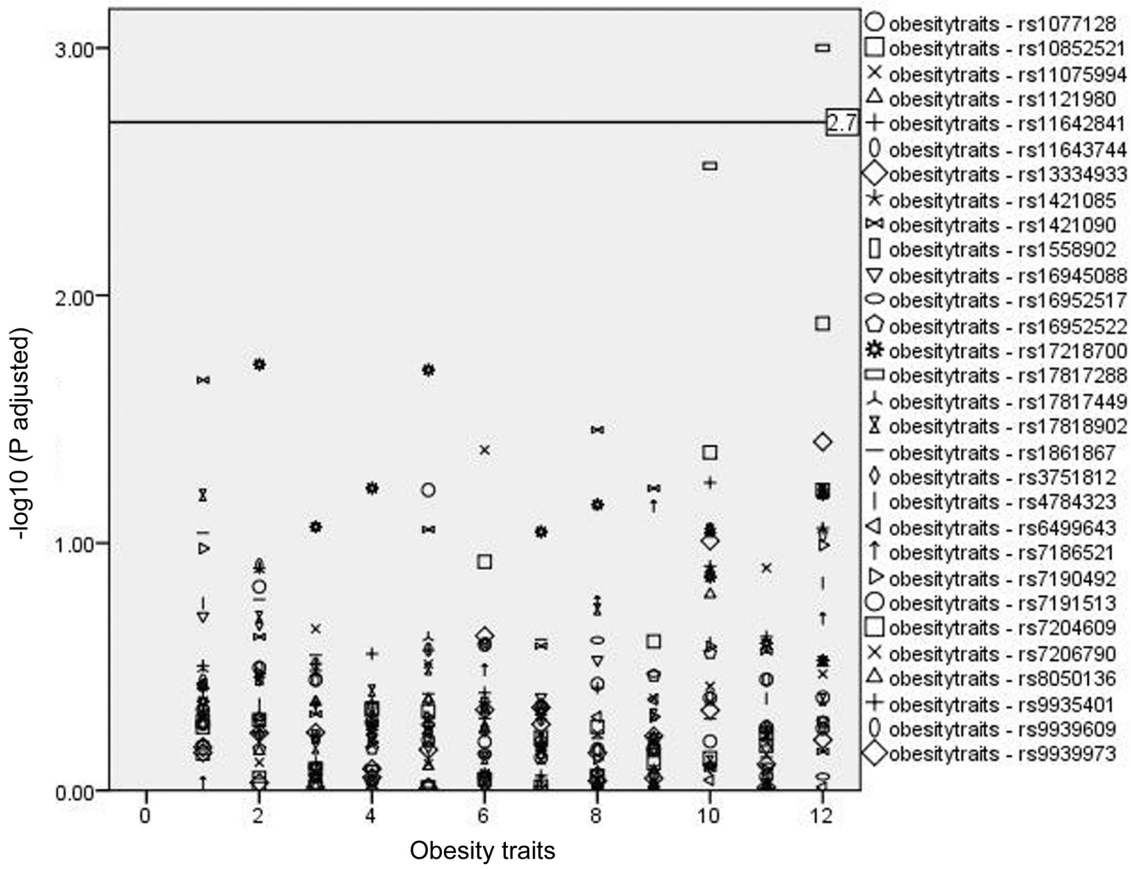

Figure 1. Log10 of the P value for single-marker association of *FTO* SNPs with obesity traits after adjustment for age and gender. X-axis: 1 = height; 2 = weight: 3 = logBMI; 4 = WC; 5 = HC; 6 = WHR; 7 = SBP; 8 = DBP; 9 = logTG; 10 = TC; 11 = HDL-C; 12 = LDL-C. For abbreviations, see legend to Table 1.

rs9939609. This indicates that the *FTO* SNPs in the first intron of the *FTO* gene are high in LD in Malaysian Malays. In our samples, three SNPs, rs9935401, rs16945088, and rs10852521 (D' = 1.0), were in complete LD with rs9939609. In the HapMap sample of Utah residents with ancestry from northern and western Europe (CEU), the three SNPs rs10852521, rs16945088, and rs9935401 are in complete LD (D' = 1.0) with rs9939609, as observed in our sample of Malaysian Malays. In contrast, in the HapMap sample of Yoruba in Ibadan, Nigeria (YRI), the rs9939609 at rs10852521 is not in strong LD (D' = 0.48). Complete LD (D = 1.0) with rs9939609 at rs16945088 and at rs17817449 has been shown in HapMap samples of African ancestry in Southwest USA (ASW); Utah residents with northern and western European ancestry (CEU); Han Chinese in Beijing, China (CHB); Chinese in Metropolitan Denver, Colorado (CHD); Gujarati Indians in Houston, Texas (GIH); Japanese in Tokyo, Japan (JPT); Luhya in Webuye, Kenya (LWK); Mexican ancestry in Los Angeles, California (MEX); Tuscans in Italy (TSI), and Yoruba in Ibadan, Nigeria (YRI). A similar LD strength was observed in our samples of Malaysian Malays. Interestingly, results from HapMap samples show that rs9939609 is in complete LD with rs10852521 with samples from Asia (JPT, CHD, and CHB), which was also replicated in our samples of Malaysian Malays. In contrast, the strength of LD of rs9939609 at rs10852521 is reduced in samples of African ancestry such as YRI, ASW, LWK, and Maasai in Kinyawa, Kenya (MKK; D > 0.35) (31).

The Singaporean Genome Variation Project analyzed the LD in 98 Singaporean Malays (MAS) with the Affymetric Genome-Wide Human SNP Array and the Illumina Human1M single-sample BeadChip genotyping platforms (29). In our study, we found that the LD pattern of all regions with complete LD in Malaysian Malays was similar to the MAS samples except for rs17218700 and rs7190492. The LD of rs17218700 with rs7190492 was lower in the MAS samples (D' = 0.74) compared with those in our study. By using the Sequenom MassARRAY® iPLEX platform with a

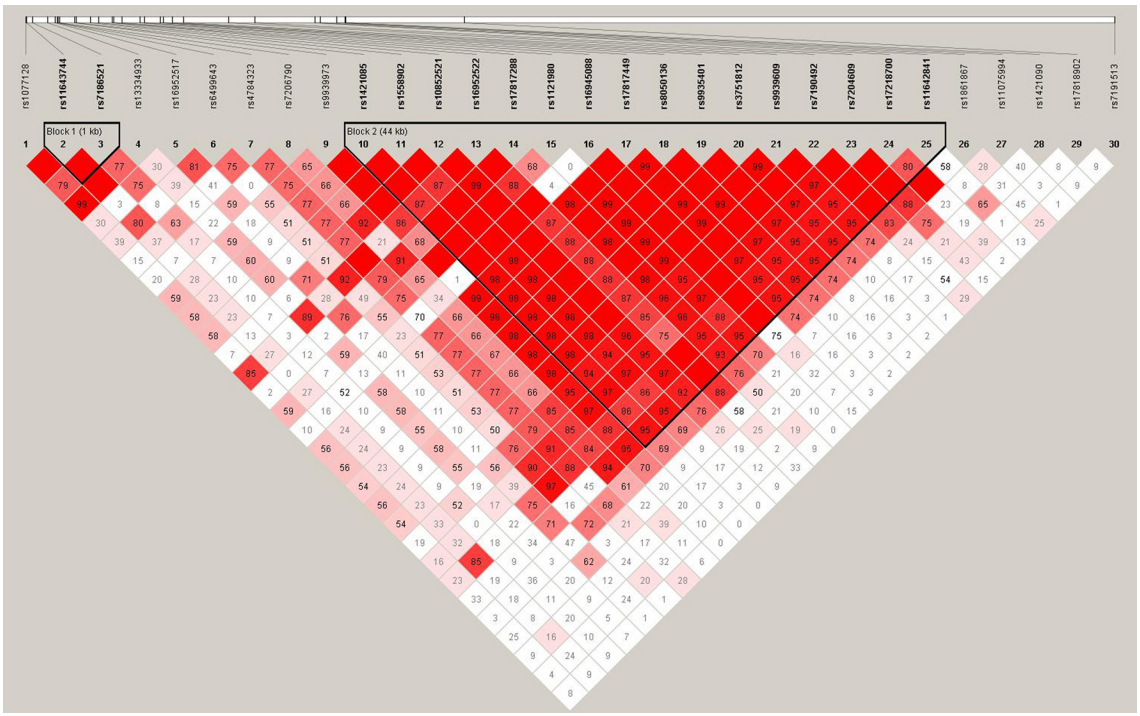

Figure 2. Linkage disequilibrium pattern of *FTO* single nucleotide polymorphisms. D prime value (D') of 100% indicates the complete LD. D' values of 100% are not shown (the box is empty). The boxes in bright red are with D' values of 100%. The boxes with values of D' < 100% are in shades of pink or red.

much larger sample size (N = 587), we found that the LD pattern from our own data for Malaysian Malays is very similar to that of the MAS samples. Therefore, we can predict a similar pattern of LD in the *FTO* gene ancestry of Malays in Southeast Asia because of the genetic homogeneity. Further studies will be needed to address this pattern in Malays in other parts of Southeast Asia.

Table 4. Haplotype analysis of the *FTO* gene.

Haplotype	Frequency	Frequencies (cases, controls)
Block 1		
GA	0.355	0.370, 0.350
AA	0.325	0.313, 0.329
AG	0.32	0.316, 0.322
Block 2		
TTCCGCATCGGTGCGC	0.324	0.330, 0.324
CACCGTAGAATAGTGA	0.139	0.130, 0.144
CACGGTAGAATAGTGC	0.138	0.152, 0.134
TTTCACATCGGTGTAC	0.131	0.114, 0.138
TTTCACATCGGTATGC	0.123	0.133, 0.121
TTCCGCGTCGGTGTGC	0.053	0.054, 0.053
TTCCATGTCGGTGTGC	0.032	0.029, 0.033
CACCGTAGAATAGTGC	0.022	0.026, 0.021

*P value was generated using 5000 permutated chi-squares. There was no significant difference in haplotype frequency of each of the haplotypes between the obese and non-obese subjects.

Differences exist in the LD structure of the *FTO* gene in diverse ethnic populations (5). For example, previous studies have shown that the degree of LD in a population with African ancestry is lower than that in European populations (32). Recent studies have reported that the genetic variability in the *FTO* gene that is in high LD are associated with a risk of obesity in Spanish (33) and African Americans (27). Our study showed novel patterns of LD in the *FTO* gene ancestry of Malaysian Malays.

Most *FTO* haplotypes were found to have frequencies of more than 5% in Malaysian Malays. We identified major haplotypes in people of Malaysian Malay ancestry that may also be present in Malays in other parts of Southeast Asia. Studies of different populations will be needed, however, to confirm this finding. The haplotypes in block 1 and block 2 of the *FTO* gene were not associated with obesity in Malaysian Malays.

Previous studies on the association of the *FTO* gene with obesity included between 240 and 5380 subjects from populations across the globe (5). Although the sample investigated in the present study was of moderate size in comparison with other studies, this study was sufficiently

powered with the population of Malaysian Malays. Since the participants of this study are middle-aged and elderly individuals, these findings cannot be generally extrapolated to children and adolescents in Malaysia. This study was conducted in Malaysian Malays, and we cannot generalize these findings to overall Malaysian populations such as Chinese, Indians and other ethnic groups in Malaysia. Therefore, large-scale genetic association studies on *FTO* should be carried out in future in other ethnic groups within the Malaysian population.

To the best of our knowledge, this is the first study on genetic variants in the *FTO* gene in Malaysian Malays. We conclude that the genetic variations in the *FTO* gene are in high LD in this ethnic group. Two haplotype blocks of *FTO* were identified, neither of which confers an increased risk for obesity in this population. We detected the association of rs17817288 with LDL-C, and this SNP may be involved in lipid metabolism in Malaysian Malays. Replication of this association in larger samples and in functional molecular studies will further increase the validity of this association and the causative relationship between the *FTO* variant and LDL-C.

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