

4.0 Results

4.1 Distribution of anthropometric and obesity-related parameters in the subjects

Genetic bias is a critical issue that should be considered in any genetic association studies. Malaysia is composed of a multiethnic population. Ethnic stratification is an important factor in any genetic studies conducted in this country with a multiethnic population. The participants in this study however, are all Malays. This is because the majority of the population from which the participants are taken from, namely, the staff of the University of Malaya, and the villagers of the Bera district, are of Malay ethnic origin. Hence, this powered the current study with the homogenous genetic background of Malays. Out of 1014 Malay participants who participated in the wellness program, only 464 participants consented to participate in this research while a total of 550 participants refused. The response rate for participation in this research was 46%. In the Bera district of Pahang, the response rate for participation in this study was about 43%. Due to lack of data on the allelic distribution of the SNPs that were included this population, the allelic frequencies from previous studies were used to estimate the sample size. Based on this sample size collected in this study, Hardy-Weinberg Equilibrium (HWE) test was performed for each SNP.

Table 4.1 shows that obesity traits and obesity-related traits such as body weight, WC, HC WHR, DBP, SBP and TG were significantly higher in obese participants compared to non-obese participants. In addition, HDL-C and height were significantly lower in obese subjects compared to non-obese subjects. The study involves adult Malaysian Malays with the mean age of 46.84 years. There was no significant difference in the leptin, adiponectin and resistin levels between obese and non-obese participants. There was a trend towards higher leptin levels in obese compared to non-

obese subjects. There was also a trend towards of lower adiponectin levels in obese compared to non-obese subjects.

Table 4.1 : Anthropometric and obesity-related parameters in the study subjects

Parameter	Pooled subjects	Non-obese	Obese	<i>p</i> Value
Age (y)	46.84±6.84	45.11±7.28 (n=500)	45.64±5.17 (n=172)	0.858
Height (m)	1.58±0.09	1.60±0.08 (n=500)	1.59±0.08 (n=172)	0.018
Weight (kg)	69.57±13.42	62.78±9.88 (n=500)	87.91±10.89 (n=172)	<0.001
BMI (kg/m ²)	27.16±4.73	24.55±3.28 (n=500)	34.55±3.10 (n=172)	<0.001
WC (cm)	88.60±11.03	85.16±10.26 (n=500)	100.45±8.51 (n=172)	<0.001
HC (cm)	102.12±9.28	98.95±8.69 (n=500)	116.71±6.44 (n=172)	<0.001
WHR	0.87±0.07	0.85±0.08 (n=500)	0.87± 0.08 (n=172)	<0.001
SBP (mm Hg)	130.71±118.56	128.58±18.11 (n=500)	136.90±18.51 (n=172)	<0.001
DBP (mm Hg)	81.73±11.97	78.13±8.06 (n=500)	84.14±9.81 (n=172)	<0.001
TC (mmol/l)	5.47±0.94	5.50±0.94 (n=347)	5.44±0.98 (n=117)	0.524
TG (mmol/l)	1.43±0.80	1.17±0.67 (n=347)	1.37±0.59 (n=117)	0.001
LDL-C (mmol/l)	3.52±0.84	3.55±0.82 (n=347)	3.47±0.87 (n=117)	0.379
HDL-C (mmol/l)	1.30±0.01	1.35±0.32 (n=347)	1.20±0.21 (n=117)	0.042
Leptin (µg/ml)	11.98±10.84	10.27±8.92 (n=22)	21.41±16.83 (n=4)	0.101
Adiponectin (µg/ml)	23.12±27.53	24.23±28.78 (n=87)	16.28±17.07 (n=14)	0.258
Resistin (ng/ml)	0.06±0.04	0.06±0.04 (n=94)	0.06±0.03 (n=80)	0.677

**p*-values were determined using T-test and Mann-Whitney U test

4.2 DNA quantification

Thermo Scientific NanoDrop™ was used to check the quality of the genomic DNA. Measurement of genomic DNA showed average yield of 58.46±59.42 ug/ml. The OD260/OD280 ratio was in average of 1.88 which indicated good quality DNA.

4.3 Genetic profiling of obesity candidate genes

Genetic profiling of the candidate genes of obesity involves single locus analysis, LD and haplotype analysis. The results for each gene in this section will be presented according to the following sequence: single locus analysis, LD and haplotype analysis. Eight candidate genes of obesity were included in this study. These genes are fat mass

and obesity associated (FTO) gene, melanocortin-4 receptor gene (MC4R), β 2-adrenoceptor gene (ADRB2), leptin gene (LEP), resistin gene (RETN), insulin-induced gene 2 (INSIG2), adiponectin gene (ADIPOQ) and syndecan 3 gene (SDC3). A total of fifty-six SNPs were genotyped. Thirty-one FTO SNPs were included in this study. Thirty FTO SNPs were in HWE and one FTO SNP deviated from HWE. Five MC4R SNPs were genotyped in which three of the MC4R SNPs were in HWE and two MC4R SNPs deviated from HWE. Five ADRB2 SNPs were genotyped in which all the SNPs were in HWE. Eight LEP SNPs were genotyped in which seven of the LEP SNPs were in HWE and one LEP SNP deviated from HWE. Three RETN SNPs were genotyped in which all the SNPs were in HWE. One INSIG2 SNP was genotyped and the INSIG2 SNP was in HWE. Two ADIPOQ SNPs were genotyped and the ADIPOQ SNPs were in HWE. One SDC3 SNP was genotyped and the SDC3 SNP deviated from HWE. The cluster plots for genotyping of all the SNPs are presented in the Appendix B. Results for the unadjusted estimates of genetic effects of the SNPs on obesity and genotype frequencies of all the SNPs are presented in the Appendix C.

4.3.1 Genetic profiling of fat mass and obesity associated (FTO) gene

A total of thirty-one FTO SNPs were genotyped in this study. Table 4.2 shows the allele frequencies in the obese and non-obese subjects for the FTO SNPs. Five-thousand permutation test was performed to the individual SNPs. The marker chromosome position, minor allele frequencies (MAF) and allele frequencies in the obese and non-obese subjects of the 30 SNPs studied in the FTO gene are summarized in Table 4.2. Following FTO SNPs did not deviate from the Hardy-Weinberg equilibrium: rs1077128, rs10852521, rs11075994, rs1121980, rs11642841, rs11643744, rs13334933, rs1421085, rs1421090, rs1558902, rs16945088, rs16952517, rs16952522, rs17218700, rs17817288, rs17817449, rs17818902, rs1861867, rs3751812, rs4784323,

rs6499643, rs7186521, rs7190492, rs7191513, rs7204609, rs7206790, rs8050136, rs9935401, rs9939609 and rs9939973; the FTO rs1861869 SNP (p HWE case: control=0.86/0.03) however, deviated from the Hardy-Weinberg equilibrium. The rs1861869 was therefore removed from further analysis. After 5000 permutation test for the 30 SNPs, there was no significant difference in allelic frequency of each of the FTO SNPs between the obese and non-obese group.

The FTO rs16945088 SNP had the lowest MAF (0.08) and FTO rs11643744 SNP had the highest MAF (0.36). MAF of 0.13 was observed for FTO rs1861867, rs11075994, rs4784323 and rs7190492 SNPs. MAF of 0.27 was observed for FTO rs10852521 and rs16952517 SNPs. MAF of 0.30 was observed in FTO rs7206790 and rs17817288 SNPs. MAF of 0.31 was observed in FTO rs1421085, rs1558902, rs17817449, rs8050136, rs3751812, rs9939609 and rs9935401 SNPs. MAF of 0.32 was observed for FTO rs7186521 and rs7191513 SNPs. MAF of 0.34 was observed for FTO rs1077128, rs13334933, rs7204609, rs9939973, rs1121980 and rs1421090 SNPs.

Table 4.2 : Allelic distribution of FTO SNPs in obese and non-obese groups

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	<i>p</i>	HWE (P ^a /P ^b)
rs1077128	53791653	0.34	G	0.67	0.67	0.03	1.00	0.14/0.52
rs11643744	53791798	0.36	G	0.37	0.37	0.43	1.00	0.79/0.74
rs7186521	53792922	0.32	A	0.68	0.68	0.03	1.00	0.13/0.89
rs13334933	53795636	0.34	A	0.67	0.67	0.13	1.00	0.21/0.56
rs16952517	53797057	0.27	A	0.30	0.30	2.50	0.92	0.54/0.52
rs6499643	53797518	0.23	T	0.80	0.80	2.16	0.97	0.97/0.42
rs4784323	53797565	0.13	G	0.87	0.87	0.03	1.00	0.30/0.47
rs7206790	53797908	0.3	G	0.30	0.30	0.01	1.00	0.39/0.94
rs9939973	53800568	0.34	A	0.35	0.35	0.05	1.00	0.28/0.52
rs1421085	53800954	0.31	C	0.31	0.31	0.09	1.00	0.21/0.45
rs1558902	53803574	0.31	A	0.31	0.31	0.09	1.00	0.21/0.45
rs10852521	53804965	0.27	C	0.74	0.74	0.09	1.00	0.34/0.84
rs16952522	53807498	0.16	G	0.17	0.17	0.74	1.00	0.72/0.21
rs17817288	53807764	0.3	G	0.71	0.72	0.10	1.00	0.56/0.86
rs1121980	53809247	0.34	T	0.35	0.35	0.02	1.00	0.78/0.62
rs16945088	53812524	0.08	A	0.92	0.92	0.02	1.00	1.00/0.49
rs17817449	53813367	0.31	G	0.32	0.32	0.20	1.00	0.13/0.89
rs8050136	53816275	0.31	A	0.31	0.31	0.09	1.00	0.21/0.77
rs9935401	53816838	0.31	A	0.32	0.37	0.13	1.00	0.13/0.82
rs3751812	53818460	0.31	T	0.31	0.31	0.09	1.00	0.21/0.77
rs9939609	53820527	0.31	A	0.32	0.32	0.16	1.00	0.13/0.77

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test with 5000 permutation test

Table 4.2, continued

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	<i>p</i>	HWE (P^a/P^b)
rs7190492	53828752	0.13	A	0.14	0.13	0.21	1.00	0.17/0.60
rs7204609	53833605	0.34	C	0.35	0.33	0.19	1.00	0.70/0.28
rs17218700	53844579	0.14	G	0.89	0.86	1.71	0.99	0.46/0.75
rs11642841	53845487	0.15	C	0.86	0.85	0.27	1.00	0.48/0.36
rs1861867	53848561	0.13	T	0.13	0.125	0.05	1.00	0.35/0.30
rs11075994	53850079	0.13	G	0.90	0.86	2.57	0.91	0.75/0.99
rs1421090	53850170	0.34	C	0.40	0.32	5.71	0.33	0.22/0.51
rs17818902	53871806	0.25	T	0.76	0.75	0.01	1.00	0.81/0.61
rs7191513	53990523	0.32	A	0.35	0.31	1.26	1.00	0.07/0.80

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test with 5000 permutation test

4.3.1.1 Genetic effects of the FTO rs1077128 on obesity in Malaysian Malays

Table 4.3 shows the genetic influence of the FTO rs1077128 variant on obesity parameters. There is no significant difference among the subjects having GG, GT and TT in all the obesity and obesity-related parameters after adjustment for age and gender. However, the GG homozygotes showed trend towards higher WHR and WC compared to GT and TT carriers. Individuals with TT genotypes showed trend towards higher weight, logBMI, HC, SBP, DBP, logTG, TC, HDL-C and LDL-C compared to GT and TT carriers.

Table 4.3 : Genetic effects of the FTO rs1077128 on obesity parameters

Parameter	GG	GT	TT	p (R ²)
Height(m)	1.58 ±0.09 (n=260)	1.59±0.09 (n=259)	1.59±0.08 (n=68)	0.54 (0.51)
Weight(kg)	68.18±14.97 (n=260)	68.41±13.34 (n=259)	70.92±13.35 (n=68)	0.32 (0.08)
LogBMI	3.28 ±0.19 (n=260)	3.29±0.18 (n=259)	3.32±0.17 (n=68)	0.36 (0.03)
WC (cm)	89.60±12.27 (n=260)	88.96±11.48 (n=259)	89.34±11.79 (n=68)	0.91 (0.06)
HC (cm)	101.60±10.29 (n=260)	102.34±9.31 (n=259)	102.85±10.70 (n=68)	0.63 (0.03)
WHR	0.88 ±0.07 (n=260)	0.87±0.08 (n=259)	0.87±0.09 (n=68)	0.26 (0.27)
SBP (mm Hg)	130.35±17.90 (n=260)	130.37±18.14 (n=259)	133.83±17.27 (n=68)	0.46 (0.07)
DBP (mm Hg)	81.74±12.63 (n=260)	82.34±11.72 (n=258)	83.01±10.44 (n=68)	0.68 (0.07)
LogTG	0.23±0.59 (n=168)	0.21±0.52 (n=187)	0.25±0.55 (n=54)	0.68 (0.13)
TC (mmol/l)	5.51±1.0 (n=168)	5.40±0.89 (n=187)	5.59±0.78 (n=54)	0.42 (0.02)
HDL-C (mmol/l)	1.30±0.29 (n=168)	1.29±0.25 (n=187)	1.33±0.28 (n=54)	0.36 (0.17)
LDL-C (mmol/l)	3.55±0.89 (n=168)	3.46±0.78 (n=187)	3.59±0.72 (n=54)	0.56 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.2 Genetic effects of the FTO rs10852521 on obesity in Malaysian Malays

FTO rs10852521 SNP, is an intronic SNP. Table 4.4 shows the genetic influence of the FTO rs10852521 variant on obesity parameters. There is a significant difference between the CC compared to CT and TT with LDL-C after adjustment for age and gender. However, after Bonferroni correction ($\alpha=0.002$), no significant difference was found between the CC compared to CT and TT with LDL-C. However, the TT homozygotes showed trend towards lower LDL-C level compared to CT and CC carriers and the CC homozygotes showed trend towards higher HDL-C compared to CT and TT carriers. The individuals with TT genotype showed trend towards higher weight, height, LogBMI, HC, WC, SBP, DBP and logTG compared to CT and CC carriers: the CT heterozygotes showed trend towards higher TC compared to CC and TT carriers.

Table 4.4 : Genetic effects of the FTO rs10852521 on obesity parameters

Parameter	CC	CT	TT	p (R ²)
Height(m)	1.58±0.07 (n=318)	1.59±0.10(n=226)	1.60±0.08 (n=43)	0.56 (0.51)
Weight(kg)	68.44±14.27 (n=318)	68.34±13.29(n=226)	71.01±16.19 (n=43)	0.52 (0.08)
LogBMI	3.29±0.19 (n=318)	3.28±0.17 (n=226)	3.30±0.20 (n=43)	0.82 (0.03)
WC (cm)	89.11±12.02(n=318)	89.12±11.11(n=226)	91.48±14.23 (n=43)	0.47 (0.06)
HC (cm)	102.22±10.25 (n=318)	101.59±9.27 (n=226)	103.60±10.43(n=43)	0.48 (0.02)
WHR	0.87±0.09 (n=318)	0.88±0.07(n=226)	0.88±0.09 (n=43)	0.90 (0.26)
SBP (mm Hg)	130.89±17.19(n=318)	130.41±18.65(n=226)	130.94±19.86 (n=43)	0.96 (0.14)
DBP (mm Hg)	82.16±11.80 (n=317)	81.81±11.70(n=226)	83.90±14.61 (n=43)	0.55 (0.07)
LogTG	0.20±0.52 (n=218)	0.25±0.58 (n=160)	0.28±0.64 (n=31)	0.78 (0.12)
TC (mmol/l)	5.46±0.91(n=218)	5.56±0.28(n=160)	5.11±0.95 (n=31)	0.74 (0.16)
HDL-C (mmol/l)	1.31±0.27(n=218)	1.30±0.40(n=160)	1.26±0.23 (n=31)	0.66 (0.14)
LDL-C (mmol/l)	3.50±0.81(n=218)	3.60±0.83(n=160)	3.13±0.73 (n=31)	0.01 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.3 Genetic effects of the FTO rs11075994 on obesity in Malaysian Malays

FTO rs11075994 SNP, is an intronic SNP. Table 4.5 shows the genetic influence of the FTO rs11075994 variant on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards higher height, WHR, SBP, DBP, TC, HDL-C and LDL-C compared to AG and AA; the AA homozygotes showed trend towards higher weight, WC, logBMI, HC and logTG compared to AG and GG carriers.

Table 4.5 : Genetic effects of the FTO rs11075994 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.60±0.11 (n=448)	1.59±0.10 (n=129)	1.59±0.09 (n=10)	0.50 (0.51)
Weight(kg)	65.77±17.95 (n=448)	68.23±13.99 (n=129)	68.76±13.99 (n=10)	0.56 (0.08)
LogBMI	3.21±0.26 (n=448)	3.27±0.17 (n=129)	3.29±0.18 (n=10)	0.22 (0.03)
WC (cm)	88.70± 11.77 (n=448)	89.06±12.08 (n=129)	89.36±11.82 (n=10)	0.91 (0.06)
HC (cm)	100.20±10.60 (n=448)	101.59±9.76 (n=129)	102.27±9.94 (n=10)	0.78 (0.02)
WHR	0.89±0.06 (n=448)	0.88±0.07 (n=129)	0.87±0.08 (n=10)	1.00 (0.25)
SBP (mm Hg)	135.10±19.70 (n=448)	130.61±18.56 (n=129)	130.64±17.73 (n=10)	0.69 (0.14)
DBP (mm Hg)	83.10±14.81 (n=447)	81.86±12.35 (n=129)	82.22±11.83 (n=10)	0.90 (0.06)
LogTG	0.15±0.46 (n=306)	0.20±0.54 (n=95)	0.23±0.56 (n=8)	0.42 (0.11)
TC (mmol/l)	5.60±0.95 (n=306)	5.52±0.90 (n=95)	5.45±0.93 (n=8)	0.44 (0.03)
HDL-C (mmol/l)	1.32±0.27 (n=306)	1.31±0.23 (n=95)	1.30±0.27 (n=8)	0.13 (0.14)
LDL-C (mmol/l)	3.70±0.84 (n=306)	3.57±0.79 (n=95)	3.49±0.84 (n=8)	0.30 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.4 Genetic effects of the FTO rs1121980 on obesity in Malaysian Malays

FTO rs1121980 SNP, is an intronic SNP. Table 4.6 shows the genetic influence of the FTO rs1121980 variant on obesity parameters. There is no significant difference among the subjects having CC, CT and TT in all the obesity and obesity-related parameters after adjustment for age and gender. The CC homozygotes showed trend towards higher logTG and HDL-C and lower WHR compared to CT and TT; the TT homozygotes showed trend towards higher height, weight, WC, HC, SBP, TC and LDL-C compared to CT and CC carriers.

Table 4.6 : Genetic effects of the FTO rs1121980 on obesity parameters

Parameter	CC	CT	TT	p (R ²)
Height(m)	1.58±0.10 (n=258)	1.58±0.09 (n=253)	1.59±0.09 (n=76)	0.54 (0.51)
Weight(kg)	68.68±14.28 (n=258)	68.23±13.18 (n=253)	69.50±16.05 (n=76)	0.69 (0.09)
LogBMI	3.29±0.17 (n=258)	3.29±0.18 (n=253)	3.29±0.21 (n=76)	0.97 (0.03)
WC (cm)	89.05±12.16 (n=258)	89.40±11.44 (n=253)	89.72±12.30(n=76)	0.96 (0.07)
HC (cm)	102.14±9.71 (n=258)	101.89±9.57 (n=253)	102.53±11.64 (n=76)	0.80 (0.03)
WHR	0.87±0.08 (n=258)	0.88±0.08 (n=253)	0.88±0.07 (n=76)	0.47 (0.26)
SBP (mm Hg)	131.43±18.79 (n=258)	129.42±17.19 (n=253)	132.53±17.21 (n=76)	0.46 (0.14)
DBP (mm Hg)	82.26±11.94 (n=258)	82.09±11.88 (n=252)	81.99±12.58 (n=76)	0.94 (0.06)
LogTG	0.23±0.57 (n=175)	0.22±0.54 (n=181)	0.20±0.56 (n=53)	0.83 (0.12)
TC (mmol/l)	5.40±0.92 (n=175)	5.49±0.89 (n=181)	5.66±1.08 (n=53)	0.16 (0.05)
HDL-C (mmol/l)	1.31±0.28 (n=175)	1.30±0.26 (n=181)	1.29±0.30 (n=53)	0.99(0.16)
LDL-C (mmol/l)	3.42±0.80 (n=175)	3.55±0.81 (n=181)	3.70±0.89 (n=53)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.5 Genetic effects of the FTO rs11642841 on obesity in Malaysian Malays

FTO rs11642841 SNP, is an intronic SNP. Table 4.7 shows the genetic influence of the FTO rs11642841 variant on obesity parameters. There is no significant difference among the subjects having CC, CA and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher height, weight, LogBMI, WC, HC, WHR, SBP and DBP compared to CA and CC carriers; the CA carriers showed trend towards higher logTG, TC and LDL-C compared to CC and AA homozygotes; the CC homozygotes showed trend towards lower HDL-C compared to CA and AA carriers.

Table 4.7 : Genetic effects of the FTO rs11642841 on obesity parameters

Parameter	CC	CA	AA	p (R ²)
Height(m)	1.58±0.09 (n=428)	1.59±0.09 (n=148)	1.60±0.11 (n=11)	0.31 (0.51)
Weight(kg)	68.30±14.04 (n=428)	69.10±14.10 (n=148)	72.96±13.81 (n=11)	0.60 (0.08)
LogBMI	3.29±0.18 (n=428)	3.29±0.18 (n=148)	3.33±0.16 (n=11)	0.33 (0.03)
WC (cm)	88.70±11.74 (n=428)	90.05±12.28 (n=148)	95.09±9.30 (n=11)	0.28 (0.06)
HC (cm)	102.11±9.91 (n=428)	101.96±9.96 (n=148)	102.82±9.33 (n=11)	0.51 (0.03)
WHR	0.87±0.07 (n=428)	0.88±0.08 (n=148)	0.93±0.05 (n=11)	0.40 (0.26)
SBP (mm Hg)	130.38±18.29 (n=428)	131.38±17.24 (n=148)	134.64±12.60 (n=11)	0.87 (0.14)
DBP (mm Hg)	81.77±12.16 (n=428)	83.15±11.36 (n=148)	83.64±13.23 (n=11)	0.39 (0.08)
LogTG	0.21±0.56 (n=295)	0.27±0.54 (n=105)	0.19±0.60 (n=8)	0.97 (0.12)
TC (mmol/l)	5.41±0.92 (n=295)	5.66±0.93 (n=106)	5.31±0.86 (n=8)	0.06 (0.04)
HDL-C (mmol/l)	1.30±0.28 (n=295)	1.31±0.26 (n=106)	1.31±0.35 (n=8)	0.24 (0.17)
LDL-C (mmol/l)	3.46±0.80 (n=295)	3.68±0.84 (n=106)	3.35±0.92 (n=8)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.6 Genetic effects of the FTO rs11643744 on obesity in Malaysian Malays

FTO rs11643744 SNP, is an intronic SNP. Table 4.8 shows the genetic influence of the FTO rs11643744 variant on obesity parameters. There is no significant difference among the subjects having AA, AG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher height, weight, WC, HC, SBP, DBP and HDL-C compared to AG and GG carriers; the AG carriers showed trend towards higher logTG and lower logBMI compared to GG and AA homozygotes; the GG homozygotes showed trend towards higher TC and LDL-C compared to AG and AA carriers.

Table 4.8 : Genetics effects of the FTO rs11643744 on obesity parameters

Parameter	AA	AG	GG	p (R ²)
Height(m)	1.59±0.09 (n=242)	1.58±0.09 (n=273)	1.58±0.10 (n=72)	0.75 (0.51)
Weight(kg)	69.34±14.20 (n=242)	67.91±13.64 (n=273)	68.62±15.40 (n=72)	0.59 (0.08)
LogBMI	3.29±0.17 (n=242)	3.28±0.19 (n=273)	3.29±0.20 (n=72)	0.72 (0.02)
WC (cm)	89.58±12.73 (n=242)	89.01±10.98 (n=273)	89.32±12.12 (n=72)	0.92 (0.06)
HC (cm)	102.56±10.10 (n=242)	101.74±9.58 (n=273)	101.78±10.46 (n=72)	0.51 (0.02)
WHR	0.87±0.09 (n=242)	0.88±0.07 (n=273)	0.88±0.08 (n=72)	0.78 (0.26)
SBP (mm Hg)	131.11±17.10 (n=242)	130.72±18.34 (n=273)	129.36±19.29 (n=72)	0.73 (0.14)
DBP (mm Hg)	82.43±11.73 (n=242)	82.02±11.30 (n=272)	81.74±15.09 (n=72)	0.91 (0.06)
LogTG	0.20±0.54 (n=176)	0.25±0.57 (n=186)	0.21±0.57 (n=47)	0.43 (0.11)
TC (mmol/l)	5.47±0.83 (n=176)	5.44±0.94 (n=186)	5.61±1.16 (n=47)	0.69 (0.02)
HDL-C (mmol/l)	1.31±0.28 (n=176)	1.29±0.26 (n=186)	1.30±0.32 (n=47)	0.56 (0.16)
LDL-C (mmol/l)	3.51±0.75 (n=176)	3.47±0.82 (n=186)	3.70±1.02 (n=47)	0.32 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.7 Genetic effects of the FTO rs1333493 on obesity in Malaysian Malays

FTO rs1333493 SNP, is an intronic SNP. Table 4.9 shows the genetic influence of the FTO rs1333493 SNP on obesity parameters. There is no significant difference among the subjects having AA, AG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher WC and WHR and lower height compared to GG and AG carriers; the AG carriers showed trend towards higher HC and lower HDL-C compared to GG and AA homozygotes; the GG homozygotes showed trend towards higher weight, logBMI, SBP, DBP, logTG, TC and LDL-C compared to AG and AA carriers.

Table 4.9 : Genetic effects of the FTO rs1333493 on obesity parameters

Parameter	AA	AG	GG	p (R ²)
Height (m)	1.58±0.09 (n=259)	1.59±0.09 (n=260)	1.59±0.08 (n=68)	0.67 (0.51)
Weight (kg)	68.26±14.95 (n=259)	68.43±13.31 (n=260)	70.44±13.32 (n=68)	0.59 (0.08)
LogBMI	3.28±0.19 (n=259)	3.29±0.18 (n=260)	3.30±0.17 (n=68)	0.58 (0.03)
WC (cm)	89.57±12.31 (n=259)	89.08±11.43 (n=260)	89.02±11.86 (n=68)	0.89 (0.06)
HC (cm)	101.60±10.28 (n=259)	102.47±9.33 (n=260)	102.43±10.60 (n=68)	0.68 (0.03)
WHR	0.88±0.07 (n=259)	0.87±0.08 (n=260)	0.87±0.09 (n=68)	0.24 (0.27)
SBP (mm Hg)	130.39±17.88 (n=259)	130.32±18.17 (n=260)	133.44±17.24 (n=68)	0.46 (0.14)
DBP (mm Hg)	81.81±12.64 (n=259)	82.20±11.74 (n=259)	83.27±10.30 (n=68)	0.71 (0.07)
LogTG	0.20±0.59 (n=169)	0.21±0.52 (n=186)	0.28±0.55 (n=54)	0.60 (0.13)
TC (mmol/l)	5.51±1.0 (n=169)	5.40±0.89 (n=186)	5.59±0.79 (n=54)	0.47 (0.02)
HDL-C (mmol/l)	1.32±0.29 (n=169)	1.30±0.25 (n=186)	1.32±0.29 (n=54)	0.78 (0.17)
LDL-C (mmol/l)	3.54±0.88 (n=169)	3.46±0.78 (n=186)	3.58±0.73 (n=54)	0.62 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.8 Genetic effects of the FTO rs1421085 on obesity in Malaysian Malays

FTO rs1421085 SNP, is an intronic SNP. Table 4.10 shows the genetic influence of the FTO rs1421085 SNP on obesity parameters. There is no significant difference among the subjects having TT, CT and CC in all the obesity and obesity-related parameters after adjustment for age and gender. The CT homozygotes showed trend towards higher HC and logTG compared to TT and CC homozygotes; the CC homozygotes showed trend towards higher height, weight, logBMI, WC, SBP, DBP, TC and LDL-C compared to CT and TT carriers.

Table 4.10 : Genetic effects of the FTO rs1421085 on obesity parameters

Parameter	TT	CT	CC	p (R ²)
Height(m)	1.58±0.09 (n=289)	1.58±0.09 (n=228)	1.60±0.08 (n=61)	0.48 (0.51)
Weight(kg)	68.29±14.32 (n=289)	68.27±13.37 (n=228)	71.18±15.17 (n=61)	0.35 (0.08)
LogBMI	3.29±0.18 (n=289)	3.29±0.18 (n=228)	3.30±0.20 (n=61)	0.61 (0.03)
WC (cm)	88.79±12.17 (n=289)	89.49±11.53 (n=228)	90.83±11.60 (n=61)	0.58 (0.07)
HC (cm)	101.95± 9.89 (n=289)	103.03±9.76 (n=228)	102.89±10.53 (n=61)	0.56 (0.03)
WHR	0.87±0.08 (n=289)	0.88±0.07(n=228)	0.88±0.07(n=61)	0.45 (0.26)
SBP (mm Hg)	131.20±18.77 (n=289)	129.65±17.38 (n=228)	132.44±15.86(n=61)	0.70 (0.14)
DBP (mm Hg)	82.21±12.05 (n=289)	81.99±11.85 (n=227)	82.49±12.31 (n=61)	1.00 (0.06)
LogTG	0.22±0.56 (n=191)	0.23±0.56 (n=172)	0.22±0.55 (n=45)	0.90 (0.12)
TC (mmol/l)	5.40±0.91 (n=191)	5.50±0.90(n=172)	5.67±1.07 (n=45)	0.09 (0.05)
HDL-C (mmol/l)	1.31±0.28(n=191)	1.30±0.26 (n=172)	1.28±0.30 (n=45)	1.00 (0.16)
LDL-C (mmol/l)	3.43±0.80 (n=191)	3.55±0.82 (n=172)	3.70±0.88(n=45)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.9 Genetic effects of the FTO rs1421090 on obesity in Malaysian Malays

FTO rs1421090 SNP, is an intronic SNP. Table 4.11 shows the genetic influence of the FTO rs1421090 SNP on obesity parameters. Significant difference was found between TT compared to CT and CC groups, with height and DBP after adjustment for age and gender. After Bonforreni correction ($\alpha=0.002$), however no significance differences were found between TT compared to CT and CC groups with height and DBP after adjustment for age and gender. The TT homozygotes showed trend towards higher SBP and DBP compared to CT and CC carriers; the CT heterozygotes showed trend towards higher TC, HDL-C and LDL-C compared CC and TT carriers; the CC homozygotes showed trend towards higher height, weight, logBMI, HC, WC and logTG and lower WHR compared to CT and TT carriers.

Table 4.11 : Genetic effects of the FTO rs1421090 on obesity parameters

Parameter	TT	CT	CC	p (R ²)
Height(m)	1.58±0.09 (n=260)	1.58±0.09 (n=250)	1.59±0.09 (n=77)	0.02 (0.52)
Weight(kg)	68.78±13.89 (n=260)	67.86±14.34 (n=250)	70.44±13.67 (n=77)	0.24 (0.08)
LogBMI	3.29±0.17 (n=260)	3.28±0.19 (n=250)	3.31±0.20 (n=77)	0.49 (0.03)
WC (cm)	88.98±10.97 (n=260)	89.35±12.53 (n=250)	90.13±12.57 (n=77)	0.54 (0.06)
HC (cm)	101.66±9.51 (n=260)	101.90±9.95 (n=250)	104.09±10.88 (n=77)	0.09 (0.02)
WHR	0.88±0.07 (n=260)	0.88±0.08 (n=250)	0.87±0.08 (n=77)	0.94 (0.26)
SBP (mm Hg)	131.72±18.70 (n=260)	129.83±17.31 (n=250)	130.21±17.35 (n=77)	0.26 (0.14)
DBP (mm Hg)	83.27±12.42 (n=260)	80.80±11.69 (n=249)	82.79±11.09 (n=77)	0.04 (0.08)
LogTG	0.24±0.54 (n=190)	0.16±0.58 (n=168)	0.35±0.50 (n=51)	0.06 (0.12)
TC (mmol/l)	5.44±0.95(n=190)	5.52±0.89 (n=168)	5.45±0.94 (n=51)	0.81 (0.02)
HDL-C (mmol/l)	1.30±0.37 (n=190)	1.33±0.27 (n=168)	1.27±0.29 (n=51)	0.27 (0.14)
LDL-C (mmol/l)	3.50±0.85 (n=190)	3.56±0.79 (n=168)	3.42±0.82 (n=51)	0.70 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.10 Genetic effects of the FTO rs1558902 on obesity in Malaysian Malays

FTO rs1558902 SNP, is an intronic SNP. Table 4.12 shows the genetic influence of the FTO rs1558902 SNP on obesity parameters. There is no significant difference among the subjects having TT, AT and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The TT homozygotes showed trend towards higher HDL-C and lower WHR compared to AT and AA carriers; the AT carriers showed trend towards higher logTG compared to AA and TT homozygotes; the AA homozygotes showed trend towards higher height, weight, logBMI, WC, HC, SBP, DBP, TC and LDL-C compared to AT and TT carriers.

Table 4.12 : Genetic effects of the FTO rs1558902 on obesity parameters

Parameter	TT	AT	AA	p (R ²)
Height(m)	1.58±0.09(n=289)	1.58±.091 (n=236)	1.60±0.08 (n=62)	0.48 (0.51)
Weight(kg)	68.29±14.32(n=289)	68.27±13.37 (n=236)	71.18±15.17 (n=62)	0.35 (0.08)
LogBMI	3.29±0.18 (n=289)	3.29±0.18 (n=236)	3.30±0.20 (n=62)	0.61 (0.03)
WC (cm)	88.79±12.17 (n=289)	89.49±11.53 (n=236)	90.33±12.77 (n=62)	0.58 (0.07)
HC (cm)	101.95±9.90 (n=289)	102.03±9.76 (n=236)	102.89±10.53 (n=62)	0.56 (0.03)
WHR	0.87±0.08 (n=289)	0.88±0.07 (n=236)	0.88±0.07 (n=62)	0.45 (0.26)
SBP (mm Hg)	131.20±18.77 (n=289)	129.65±17.38 (n=236)	132.44±15.86 (n=62)	0.70 (0.14)
DBP (mm Hg)	82.21±12.05 (n=289)	81.99±11.85 (n=235)	82.49±12.31 (n=62)	1.00 (0.06)
LogTG	0.22±0.56 (n=192)	0.23±0.56 (n=172)	0.22±0.55 (n=45)	0.90 (0.12)
TC (mmol/l)	5.40±.91 (n=192)	5.50±1.00 (n=172)	5.67±1.07 (n=45)	0.09 (0.05)
HDL-C (mmol/l)	1.31±0.28 (n=192)	1.30±0.26 (n=172)	1.28±0.30 (n=45)	1.00 (0.16)
LDL-C (mmol/l)	3.43±0.80 (n=192)	3.55±0.82 (n=172)	3.70±0.88 (n=45)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.11 Genetic effects of the FTO rs16945088 on obesity in Malaysian Malays

FTO rs16945088 SNP, is an intronic SNP. Table 4.13 shows the genetic influence of the FTO rs16945088 SNP on obesity parameters. There is no significant difference among the subjects having AA, AG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher height, weight, WC, HC, WHR, SBP and DBP compared to AG and GG carriers; the AG carriers showed trend towards higher TC and LDL-C compared to AA and GG carriers; the GG homozygotes showed trend towards higher logTG, and HDL-C and lower logBMI compared to AA and AG carriers.

Table 4.13 : Genetic effects of the FTO rs16945088 on obesity parameters

Parameter	AA	AG	GG	p (R ²)
Height(m)	1.59±0.09 (n=491)	1.57±0.09 (n=93)	1.57±0.02 (n=3)	0.20 (0.51)
Weight(kg)	68.92±13.92 (n=491)	67.14±14.62 (n=93)	60.73±15.72 (n=3)	0.60 (0.08)
LogBMI	3.29±0.18 (n=491)	3.29±0.18 (n=93)	3.18±0.30 (n=3)	0.87 (0.03)
WC (cm)	89.50±11.78 (n=491)	88.36±12.00 (n=93)	84.33±21.46 (n=3)	0.61 (0.00)
HC (cm)	102.25±9.76 (n=491)	101.42±10.59 (n=93)	96.33±11.59 (n=3)	0.67 (0.03)
WHR	0.88±0.08 (n=491)	0.87±0.08 (n=93)	0.87±0.14 (n=3)	0.89 (0.26)
SBP (mm Hg)	131.04±17.84 (n=,491)	129.16±18.57 (n=93)	127.00±15.40 (n=3)	0.42 (0.14)
DBP (mm Hg)	82.36±12.21 (n=491)	81.36±10.66 (n=92)	74.00±12.17 (n=3)	0.30 (0.07)
LogTG	0.23±0.56 (n=349)	0.19±0.55 (n=58)	0.47±0.00 (n=1)	0.68 (0.11)
TC (mmol/l)	5.46±0.94(n=349)	5.53±0.84 (n=58)	5.40±0.00 (n=1)	0.81 (0.02)
HDL-C (mmol/l)	1.30±0.28 (n=349)	1.28±0.25 (n=58)	1.49±0.00 (n=1)	0.68 (0.17)
LDL-C (mmol/l)	3.50±0.83 (n=349)	3.62±0.73 (n=58)	3.18±0.00 (n=1)	0.52 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.12 Genetic effects of the FTO rs16952517 on obesity in Malaysian Malays

FTO rs16952517 SNP, is an intronic SNP. Table 4.14 shows the genetic influence of the FTO rs16952517 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards higher WHR compared to AG and AA carriers; the AG carriers showed trend towards higher WC, SBP, logTG, TC and HDL-C compared to AA and GG carriers; the AA homozygotes showed trend towards higher weight, logBMI, DBP and LDL-C and lower weight and HC compared to AG and GG carriers.

Table 4.14 : Genetic effects of the FTO rs16952517 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=317)	1.59±0.09 (n=223)	1.59±0.10 (n=47)	0.65 (0.51)
Weight(kg)	68.40±13.93 (n=317)	68.45±14.09 (n=223)	70.50±14.72 (n=47)	0.51 (0.08)
LogBMI	27.09±4.85 (n=317)	27.43±5.20 (n=223)	27.46±5.49 (n=47)	0.87 (0.03)
WC (cm)	89.29±11.69 (n=317)	89.45±12.34 (n=223)	88.45±10.78 (n=47)	0.82 (0.06)
HC (cm)	101.56±10.99 (n=317)	103.66±22.90 (n=223)	103.66±9.24 (n=47)	0.54 (0.02)
WHR	0.90±0.46 (n=317)	0.87±0.09 (n=223)	0.86±0.06 (n=47)	0.72 (0.04)
SBP (mm Hg)	130.51±18.62 (n=317)	131.37±18.40 (n=223)	130.94±15.58 (n=47)	0.66 (0.13)
DBP (mm Hg)	82.83±12.37 (n=316)	82.37±12.21 (n=223)	84.32±9.87 (n=47)	0.25 (0.07)
LogTG (mmol/l)	0.22±0.58 (n=212)	0.25±0.52 (n=160)	0.15±0.59 (n=37)	0.34 (0.12)
TC (mmol/l)	5.44±0.88 (n=212)	5.51±0.98 (n=160)	5.47±0.92 (n=37)	0.79 (0.02)
HDL-C (mmol/l)	1.30±0.36 (n=212)	1.33±0.28 (n=160)	1.29±0.31 (n=37)	0.80 (0.13)
LDL-C (mmol/l)	3.51±0.76 (n=212)	3.51±0.88 (n=160)	3.56±0.87 (n=37)	0.88 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.13 Genetic effects of the FTO rs16952522 on obesity in Malaysian Malays

FTO rs16952522 SNP, is an intronic SNP. Tables 4.15 shows the genetic influence of the FTO rs16952522 SNP on obesity parameters. There is no significant difference among the subjects having CC, CG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The CC homozygotes showed trend towards higher DBP and lower height compared to CG and GG carriers; the CG carriers showed trend towards higher weight, logBMI and HC compared to CC and GG homozygotes; the GG homozygotes showed trend towards higher WHR, SBP, logTG, TC and LDL-C compared to CC and CG carriers.

Table 4.15 : Genetic effects of the FTO rs16952522 on obesity parameters

Parameter	CC	CG	GG	p (R ²)
Height(m)	1.58±0.09(n=429)	1.59±0.09(n=149)	1.59±0.09(n=17)	0.65 (0.51)
Weight(kg)	68.21±13.94 (n=429)	69.64±14.56 (n=149)	68.84±12.27 (n=17)	0.68 (0.08)
LogBMI	3.29±0.18 (n=429)	3.30±0.20 (n=149)	3.29±0.16 (n=17)	0.88 (0.03)
WC (cm)	89.08±12.15 (n=429)	89.82±11.20 (n=149)	89.82±10.52 (n=17)	0.68 (0.02)
HC (cm)	101.85±9.71 (n=429)	102.90±10.65 (n=149)	100.88±7.78 (n=17)	0.95 (0.01)
WHR	0.87±0.08 (n=429)	0.87±0.06 (n=149)	0.89±0.06 (n=17)	0.71 (0.26)
SBP (mm Hg)	131.21±18.54 (n=429)	128.86±16.27 (n=149)	134.35±15.53 (n=17)	0.63 (0.14)
DBP (mm Hg)	82.46±11.74 (n=420)	81.36±12.70 (n=149)	81.59±11.85 (n=17)	0.85 (0.06)
LogTG	0.24±0.56 (n=286)	0.17±0.54 (n=111)	0.38±0.64 (n=12)	0.34 (0.12)
TC (mmol/l)	5.47±0.91 (n=286)	5.45±0.91 (n=111)	5.84±1.40 (n=12)	0.28 (0.03)
HDL-C (mmol/l)	1.30±0.28 (n=286)	1.30±0.26 (n=111)	1.20±0.34 (n=12)	0.55 (0.16)
LDL-C (mmol/l)	3.50±0.81 (n=286)	3.52±0.80 (n=111)	3.78±1.08 (n=12)	0.53 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.14 Genetic effects of the FTO rs17218700 on obesity in Malaysian Malays

FTO rs17218700 SNP, is an intronic SNP. Table 4.16 shows the genetic influence of the FTO rs17218700 SNP on obesity parameters. There is significant difference between the GG compared to AG and AA, with weight and HC after adjustment for age and gender. However, after Bonferroni correction ($\alpha=0.002$), no significant difference was found between the GG compared to AG and AA with weight and HC. The AA homozygotes showed trend towards higher height, weight, WC, WHR and HDL-C compared to AG and GG carriers. The AA homozygotes showed trend towards lower HC compared to AG and GG carrier. The GG homozygotes showed trend towards higher logBMI, SBP, DBP and logTG compared to AG and AA carriers; the AG carriers showed trend towards higher TC and LDL-C compared to AA and GG homozygotes.

Table 4.16 : Genetic effects of the FTO rs17218700 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=439)	1.59±0.09 (n=137)	1.60±0.08 (n=11)	0.44 (0.51)
Weight(kg)	68.95±14.40 (n=439)	66.86±12.34(n=137)	76.17±17.56 (n=11)	0.02 (0.01)
LogBMI	3.36±0.17 (n=439)	3.26±0.17 (n=137)	3.30±0.18 (n=11)	0.09 (0.03)
WC (cm)	89.47±11.76 (n=439)	88.27±11.44 (n=137)	95.00±19.00 (n=11)	0.06 (0.07)
HC (cm)	108.70±11.98 (n=439)	100.50±9.512 (n=137)	102.42±9.89 (n=11)	0.02 (0.03)
WHR	0.87±0.11 (n=439)	0.88±0.07 (n=137)	0.89±0.08 (n=11)	0.86 (0.26)
SBP (mm Hg)	134.25±18.32 (n=439)	128.44±18.40 (n=137)	131.33±17.75 (n=11)	0.09 (0.14)
DBP (mm Hg)	87.40±14.18 (n=438)	81.08±11.31 (n=137)	82.37±12.11 (n=11)	0.07 (0.07)
LogTG	0.29±0.37 (n=307)	0.27±0.61 (n=96)	0.21±0.54 (n=6)	0.61 (0.12)
TC (mmol/l)	5.47±0.94 (n=307)	5.53±0.89 (n=96)	4.72±0.50 ±(n=6)	0.14 (0.03)
HDL-C (mmol/l)	1.11±0.09 (n=307)	1.29±0.28 (n=96)	1.31±0.27 (n=6)	0.25 (0.16)
LDL-C (mmol/l)	3.45±0.82 (n=307)	3.53±0.78 (n=96)	2.96±0.35 (n=6)	0.30 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.15 Genetic effects of the FTO rs17817288 on obesity in Malaysian Malays

FTO rs17817288 SNP, is an intronic SNP. Table 4.17 shows the genetic influence of the FTO rs17817288 SNP on obesity parameters. There is a significant difference between GG compared to AG and AA groups, with TC and LDL-C levels after adjustment for age and gender. However, after Bonferroni correction ($\alpha=0.002$), there is a significant difference between the GG compared to AG and AA groups with LDL-C but not with TC. The AA homozygotes had significantly lower LDL-C levels compared to AG and GG carriers. The AA homozygotes showed trend towards lower logBMI, TC and HDL-C compared to AG and GG carriers. The GG homozygotes showed trend towards higher HC compared to AA and AG carriers; the AA homozygotes showed trend towards higher height, weight, WC, WHR, SBP, DBP and logTG compared to GG and AG carriers.

Table 4.17 : Genetic effects of the FTO rs17817288 on obesity parameters

Parameter	GG	AG	AA	P (R ²)
Height(m)	1.58±0.09 (n=289)	1.59±0.10 (n=245)	1.60±0.08 (n=53)	0.73 (0.51)
Weight(kg)	68.77±13.94 (n=289)	68.26±13.79 (n=245)	69.12±15.95 (n=53)	0.87 (0.07)
LogBMI	3.29±0.18 (n=289)	3.29±0.18 (n=245)	3.27±0.21 (n=289)	0.80 (0.03)
WC (cm)	89.40±11.86 (n=289)	89.94±11.30 (n=245)	90.23±14.24 (n=53)	0.81 (0.06)
HC (cm)	102.23±9.78 (n=289)	101.91±9.91 (n=245)	102.06±10.66 (n=53)	0.94 (0.02)
WHR	0.87±0.08 (n=289)	0.87±0.07 (n=245)	0.88±0.08 (n=53)	0.88 (0.26)
SBP (mm Hg)	130.96±16.94 (n=289)	130.37±18.56 (n=245)	130.97±20.48 (n=53)	0.99 (0.14)
DBP (mm Hg)	82.27±11.79 (n=288)	81.81±11.44 (n=245)	83.06±15.17 (n=53)	0.86 (0.07)
LogTG	1.42± 0.81 (n=206)	1.49±0.92 (n=165)	1.52±0.91 (n=38)	0.70 (0.10)
TC (mmol/l)	5.44±0.91 (n=206)	5.60±0.93 (n=165)	5.07±0.90 (n=38)	0.00 (0.05)
HDL-C (mmol/l)	1.31±0.27 (n=206)	1.30±0.28 (n=165)	1.25±0.24 (n=38)	0.57 (0.16)
LDL-C (mmol/l)	3.48±0.80 (n=206)	3.65±0.85 (n=165)	3.13±0.69 (n=38)	0.001* (0.04)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.16 Genetic effects of the FTO rs17817449 on obesity in Malaysian Malays

FTO rs17817449 SNP, is an intronic SNP. Table 4.18 shows the genetic influence of the FTO rs17817449 SNP on obesity parameters. There is no significant difference among the subjects having TT, GT and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The GT homozygotes showed trend towards higher DBP and HDL-C compared to TT and GG carriers; the GG homozygotes showed trend towards higher height, weight, logBMI, WC, HC, SBP, logTG, TC and LDL-C compared to GT and TT carriers; the TT homozygotes showed trend towards lower WHR compared to GT and GG carriers.

Table 4.18 : Genetic effects of the FTO rs17817449 on obesity parameters

Parameter	TT	GT	GG	p (R ²)
Height(m)	1.58±0.09 (n=287)	1.58±0.09 (n=240)	1.60±0.08 (n=60)	0.32 (0.51)
Weight(kg)	68.13±14.37 (n=287)	68.02±13.30 (n=240)	72.18±15.04 (n=60)	0.13 (0.09)
LogBMI	3.29±0.18 (n=287)	3.29±0.18 (n=240)	3.31±0.20 (n=60)	0.34 (0.03)
WC (cm)	88.80±12.22 (n=287)	89.39±11.50 (n=240)	91.20±11.45 (n=60)	0.48 (0.07)
HC (cm)	101.94±9.94 (n=287)	101.83±9.62 (n=240)	103.73±10.78 (n=60)	0.24 (0.03)
WHR	0.87±0.08 (n=287)	0.88±0.07 (n=240)	0.88±0.07 (n=60)	0.47 (0.26)
SBP (mm Hg)	131.15±18.84 (n=287)	129.76±17.28 (n=240)	132.41±15.94 (n=60)	0.67 (0.14)
DBP (mm Hg)	82.13±12.07 (n=287)	82.23±11.92 (n=239)	82.00±12.01 (n=60)	0.94 (0.06)
LogTG (mmol/l)	0.22±0.56 (n=190)	0.22±0.56 (n=173)	0.23±0.55 (n=46)	1.00 (0.13)
TC (mmol/l)	5.40±0.91 (n=190)	5.51±0.90 (n=173)	5.65±1.07 (n=46)	0.13 (0.05)
HDL-C (mmol/l)	1.30±0.28 (n=190)	1.32±0.26 (n=173)	1.27±0.30 (n=46)	0.96 (0.16)
LDL-C (mmol/l)	3.43±0.80 (n=190)	3.56±0.82 (n=173)	3.68±0.88 (n=46)	0.09 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.17 Genetic effects of the FTO rs17818902 on obesity in Malaysian Malays

FTO rs17818902 SNP, is an intronic SNP. Table 4.19 shows the genetic influence of the FTO rs17818902 SNP on obesity parameters. There is no significant difference among the subjects having TT, GT and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The TT homozygotes showed trend towards higher weight, logBMI, WC, HC, WHR and HDL-C compared to GT and GG carriers; the GT carriers showed trend towards higher SBP, DBP and LDL-C compared to TT and GG homozygotes; the GG homozygotes showed trend towards higher logTG and TC and lower height compared to GT and TT carriers.

Table 4.19 : Genetic effects of the FTO rs17818902 on obesity parameters

Parameter	TT	GT	GG	p (R ²)
Height(m)	1.59±0.10 (n=333)	1.59±0.09 (n=220)	1.55±0.07 (n=34)	0.06 (0.52)
Weight(kg)	69.42±14.72 (n=333)	67.83±12.79 (n=220)	65.43±14.62 (n=34)	0.20 (0.08)
LogBMI	3.29±0.19 (n=333)	3.28±0.17 (n=220)	3.28±0.20 (n=34)	0.67 (0.03)
WC (cm)	89.78±11.98 (n=333)	89.00±11.52 (n=220)	86.36±12.61 (n=34)	0.40 (0.06)
HC (cm)	102.46±10.02 (n=333)	101.83±9.55 (n=220)	100.04±10.89 (n=34)	0.32 (0.02)
WHR	0.88±0.08 (n=333)	0.87±0.08 (n=220)	0.86±0.08 (n=34)	0.74 (0.26)
SBP (mm Hg)	130.44±17.06 (n=333)	131.72±19.07 (n=220)	127.03±18.66 (n=34)	0.62 (0.14)
DBP (mm Hg)	81.65±12.13 (n=333)	83.40±11.58 (n=219)	79.29±12.45 (n=34)	0.19 (0.17)
LogTG	0.23±0.57 (n=235)	0.20±0.55 (n=151)	0.29±0.50 (n=23)	0.49 (0.11)
TC (mmol/l)	5.46±0.88 (n=235)	5.48±0.96 (n=151)	5.50±1.16 (n=23)	0.76 (0.03)
HDL-C (mmol/l)	1.31±0.29 (n=235)	1.28±0.25 (n=151)	1.28±0.27 (n=23)	0.55 (0.17)
LDL-C (mmol/l)	3.47±0.79 (n=235)	3.57±0.83 (n=151)	3.53±1.02 (n=23)	0.43 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.18 Genetic effects of the FTO rs1861867 on obesity in Malaysian Malays

FTO rs1861867 SNP, is an intronic SNP. Table 4.20 shows the genetic influence of the FTO rs1861867 SNP on obesity parameters. There is no significant difference among the subjects having CC, CT and TT in all the obesity and obesity-related parameters after adjustment for age and gender. The CC homozygotes showed trend towards higher HDL-C compared to CT and TT carriers; the CT heterozygotes showed trend towards higher weight, logBMI, WC, WHR, SBP, DBP, TC and LDL-C compared CC and TT homozygotes; the TT homozygotes showed trend towards higher height, HC and logTG compared to CT and CC carriers.

Table 4.20 : Genetic effects of the FTO rs1861867 on obesity parameters

Parameter	CC	CT	TT	p (R ²)
Height(m)	1.58±0.09 (n=452)	1.59±0.09 (n=122)	1.61±0.09 (n=13)	0.09 (0.51)
Weight(kg)	68.03±14.00 (n=452)	70.84±14.22 (n=122)	70.67±14.12 (n=13)	0.17 (0.08)
LogBMI	3.29±0.18 (n=452)	3.31±0.18 (n=122)	3.25±0.20 (n=13)	0.28 (0.03)
WC (cm)	88.95±12.02 (n=452)	90.48±11.66 (n=122)	89.54±6.67 (n=13)	0.57 (0.04)
HC (cm)	101.80±10.09 (n=452)	102.97±9.51 (n=122)	103.46±6.28 (n=13)	0.41 (0.02)
WHR	0.87±0.08 (n=452)	0.88±0.08 (n=122)	0.87±0.05 (n=13)	0.88 (0.26)
SBP (mm Hg)	130.20±17.31 (n=452)	133.07±20.23 (n=122)	126.38±15.03 (n=13)	0.25 (0.14)
DBP (mm Hg)	81.85±11.68 (n=451)	83.26±13.23 (n=122)	82.15±9.76 (n=13)	0.61 (0.06)
LogTG	0.21±0.54 (n=309)	0.26±0.60 (n=89)	0.39±0.60 (n=11)	0.64 (0.11)
TC (mmol/l)	5.47±0.90 (n=309)	5.50±1.03 (n=89)	5.20±0.74 (n=11)	0.51 (0.05)
HDL-C (mmol/l)	1.31±0.28 (n=309)	1.29±0.23 (n=89)	1.26±0.28 (n=11)	0.73 (0.17)
LDL-C (mmol/l)	3.52±0.80 (n=309)	3.53±0.90 (n=89)	3.16±0.72 (n=11)	0.31 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.19 Genetic effects of the FTO rs3751812 on obesity in Malaysian Malays

FTO rs3751812 SNP, is an intronic SNP. Table 4.21 shows the genetic influence of the FTO rs3751812 SNP on obesity parameters. There is no significant difference among the subjects having GG, GT and TT in all the obesity and obesity-related parameters after adjustment for age and gender. The GT carriers showed trend towards higher HDL-C compared to GG and TT homozygotes; the TT homozygotes showed trend towards higher height, weight, logBMI, WC, HC, SBP, DBP, logTG, TC and LDL-C compared to GT and GG carriers. The GG homozygotes showed trend towards lower WHR compared to GT and TT carriers.

Table 4.21 : Genetic effects of the FTO rs3751812 on obesity parameters

Parameter	GG	GT	TT	p (R²)
Height(m)	1.58±0.09 (n=287)	1.58±0.09 (n=240)	1.60±0.09 (n=60)	0.38 (0.51)
Weight(kg)	68.35±14.35 (n=287)	68.08±13.36 (n=240)	71.76±15.01 (n=60)	0.21 (0.09)
LogBMI	3.28±0.18 (n=287)	3.29±0.18 (n=240)	3.31±0.19 (n=60)	0.44 (0.03)
WC (cm)	88.82±12.20 (n=287)	89.39±11.52 (n=240)	91.11±11.47 (n=60)	0.53 (0.07)
HC (cm)	101.96±9.93 (n=287)	101.96±9.73 (n=240)	103.17±10.51 (n=60)	0.43 (0.03)
WHR	0.87±0.08 (n=287)	0.88±0.07 (n=240)	0.88±0.07 (n=60)	0.55 (0.26)
SBP (mm Hg)	131.18±18.83(n=287)	129.54±17.20 (n=240)	133.10±16.19 (n=60)	0.48 (0.14)
DBP (mm Hg)	82.15±12.05 (n=287)	82.16±12.95 (n=240)	82.17±11.96 (n=60)	0.97 (0.06)
LogTG	0.22±0.56 (n=190)	0.22±0.55 (n=173)	0.23±0.55 (n=46)	0.96 (0.12)
TC (mmol/l)	5.40±0.91 (n=190)	5.50±0.90 (n=173)	5.67±1.06 (n=46)	0.09 (0.05)
HDL-C (mmol/l)	1.30±0.28 (n=190)	1.31±0.26 (n=173)	1.27±0.30 (n=46)	0.95 (0.16)
LDL-C (mmol/l)	3.44±0.80 (n=190)	3.54±0.82 (n=173)	3.71±0.87 (n=46)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.20 Genetic effects of the FTO rs4784323 on obesity in Malaysian Malays

FTO rs4784323 SNP, is an intronic SNP. Table 4.22 shows the genetic influence of the FTO rs4784323 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards higher HDL-C compared to AG and AA carriers; the AG heterozygotes showed trend towards higher TC and LDL-C compared to AA and GG homozygotes; the AA homozygotes showed trend towards higher height, weight, logBMI, WC, HC, WHR, SBP, DBP and logTG compared to AG and GG carriers.

Table 4.22 : Genetic effects of the FTO rs4784323 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=448)	1.58±0.10 (n=126)	1.63±0.06 (n=13)	0.18 (0.51)
Weight(kg)	68.56±13.86 (n=448)	68.16±15.14 (n=126)	73.87±7.74 (n=13)	0.45 (0.08)
LogBMI	3.29±0.18 (n=448)	3.28±0.18 (n=126)	3.32±0.11 (n=13)	0.77 (0.03)
WC (cm)	89.08±11.46 (n=448)	89.61±13.57 (n=126)	93.23±6.14 (n=13)	0.52 (0.06)
HC (cm)	102.00±9.99 (n=448)	102.24±10.06 (n=126)	103.31±4.23 (n=13)	0.74 (0.02)
WHR	0.87±0.07 (n=448)	0.88±0.09 (n=126)	0.90±0.05 (n=13)	0.58 (0.26)
SBP (mm Hg)	130.57±17.75 (n=448)	131.35±18.53 (n=126)	131.54±19.56 (n=13)	0.96 (0.14)
DBP (mm Hg)	81.94±11.49 (n=448)	82.63±13.66 (n=126)	84.92±11.53 (n=13)	0.84 (0.07)
LogTG	0.21±0.54 (n=316)	0.23±0.55 (n=80)	0.42±0.57 (n=13)	0.64 (0.01)
TC (mmol/l)	5.48±0.91 (n=316)	5.50±0.98 (n=80)	5.09±0.92 (n=13)	0.25 (0.03)
HDL-C (mmol/l)	1.31±0.28 (n=316)	1.30±0.24 (n=80)	1.19±0.23 (n=13)	0.43 (0.17)
LDL-C (mmol/l)	3.52±0.80 (n=316)	3.56±0.87 (n=80)	3.10±0.82 (n=13)	0.15 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.21 Genetic effects of the FTO rs6499643 on obesity in Malaysian Malays

FTO rs6499643 SNP, is an intronic SNP. Table 4.23 shows the genetic influence of the FTO rs6499643 SNP on obesity parameters. There is no significant difference among the subjects having TT, CT and CC in all the obesity and obesity-related parameters after adjustment for age and gender. The TT homozygotes showed trend towards higher SBP and DBP compared to CT and CC carriers; the CT heterozygotes showed trend towards higher WC, WHR, TC, LDL-C, and HDL-C compared to CT and CC homozygotes; the CC homozygotes showed trend towards higher weight, logBMI, HC and logTG compared to CT and CC carriers.

Table 4.23 : Genetic effects of the FTO rs6499643 on obesity parameters

Parameter	TT	CT	CC	p (R ²)
Height(m)	1.58±0.09 (n=350)	1.59±0.09 (n=210)	1.59±0.08 (n=27)	0.37 (0.51)
Weight(kg)	68.85±14.42 (n=350)	68.08±13.76 (n=210)	69.22±11.32 (n=27)	0.52 (0.08)
LogBMI	3.29±0.19 (n=350)	3.28±0.18 (n=210)	3.30±0.12 (n=27)	0.80 (0.03)
WC (cm)	89.13±12.07 (n=350)	89.74±11.60 (n=210)	87.72±11.18 (n=27)	0.92 (0.06)
HC (cm)	102.43±10.05 (n=350)	101.33±9.72 (n=210)	103.60±9.18 (n=27)	0.59 (0.03)
WHR	0.87±0.09 (n=350)	0.89±0.07 (n=210)	0.85±0.10 (n=27)	0.26 (0.26)
SBP (mm Hg)	131.07±17.63 (n=350)	130.35±18.47 (n=210)	128.86±17.99 (n=27)	0.66 (0.14)
DBP (mm Hg)	82.46±12.66 (n=350)	81.69±10.86 (n=209)	81.76±11.61 (n=27)	0.50 (0.06)
LogTG	0.21±0.55 (n=241)	0.23±0.56 (n=150)	0.32±0.58 (n=18)	0.43 (0.12)
TC (mmol/l)	5.46±0.98 (n=241)	5.49±0.85 (n=150)	5.47±0.75 (n=18)	0.91 (0.02)
HDL-C (mmol/l)	1.30±0.27 (n=241)	1.31±0.29 (n=150)	1.26±0.25 (n=18)	0.62 (0.16)
LDL-C (mmol/l)	3.51±0.87 (n=241)	3.52±0.76 (n=150)	3.47±0.57 (n=18)	0.97 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.22 Genetic effects of the FTO rs7186521 on obesity in Malaysian Malays

FTO rs7186521 SNP, is an intronic SNP. Table 4.24 shows the genetic influence of the FTO rs7186521 SNP on obesity parameters. There is no significant difference among the subjects having AA, AG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher TC and LDL-C compared to AG and GG carriers; the AG heterozygotes showed trend towards higher HDL-C and lower height compared to AA and GG homozygotes; the GG homozygotes showed trend towards higher weight, logBMI, WC, HC, WHR, SBP, DBP and logTG compared to AG and AA carriers.

Table 4.24 : Genetic effects of the FTO rs7186521 on obesity parameters

Parameter	AA	AG	GG	p (R ²)
Height(m)	1.59±0.09 (n=276)	1.58±0.09 (n=246)	1.59±0.10 (n=65)	0.93 (0.51)
Weight(kg)	68.91±14.00 (n=276)	67.67±13.29 (n=246)	70.73±16.76 (n=65)	0.36 (0.08)
LogBMI	3.29±0.19 (n=276)	3.28±0.17 (n=246)	3.31±0.19 (n=65)	0.46 (0.03)
WC (cm)	88.77±11.37 (n=276)	89.35±11.96 (n=246)	91.18±13.40 (n=65)	0.61 (0.06)
HC (cm)	102.26±10.11 (n=276)	101.69±9.26 (n=246)	102.84±11.36 (n=65)	0.58 (0.03)
WHR	0.87±0.07 (n=276)	0.88±0.08 (n=246)	0.89±0.07 (n=65)	0.33 (0.26)
SBP (mm Hg)	130.74±19.00 (n=276)	130.42±16.89 (n=246)	131.71±17.34 (n=65)	0.91 (0.14)
DBP (mm Hg)	82.66±12.47 (n=275)	81.09±11.51 (n=246)	84.06±11.41 (n=65)	0.17 (0.07)
LogTG	0.27±0.56 (n=196)	0.14±0.54 (n=173)	0.33±0.59 (n=40)	0.07 (0.13)
TC (mmol/l)	5.55±0.95 (n=196)	5.37±0.91 (n=173)	5.51±0.84 (n=40)	0.13 (0.04)
HDL-C (mmol/l)	1.29±0.27 (n=196)	1.31±0.26 (n=173)	1.29±0.32 (n=40)	0.60 (0.17)
LDL-C (mmol/l)	3.58±0.83 (n=196)	3.44±0.81 (n=173)	3.50±0.80 (n=40)	0.20 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.23 Genetic effects of the FTO rs7190492 on obesity in Malaysian Malays

FTO rs7190492 SNP, is an intronic SNP. Table 4.25 shows the genetic influence of the FTO rs7190492 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The AG heterozygotes showed trend towards higher TC and LDL-C compared to AA and GG homozygotes; the AA homozygotes showed trend towards higher weight, height, logBMI, WC, HC, SBP, DBP and logTG and lower HDL-C compared to AG and GG carriers; the GG homozygotes showed trend towards lower WHR compared to AG and AA carriers.

Table 4.25 : Genetic effects of the FTO rs7190492 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=449)	1.59±0.10 (n=125)	1.61±0.06 (n=13)	0.11 (0.51)
Weight(kg)	68.14±13.88 (n=449)	69.88±14.68 (n=125)	71.72±13.68 (n=13)	0.34 (0.01)
LogBMI	3.29±0.18 (n=449)	3.29±0.18 (n=125)	3.30±0.20 (n=13)	0.81 (0.03)
WC (cm)	89.03±11.92 (n=449)	89.97±12.09 (n=125)	91.69±6.28 (n=13)	0.64 (0.06)
HC (cm)	101.90±10.14 (n=449)	101.48±9.36 (n=125)	104.62±5.58 (n=13)	0.51 (0.03)
WHR	0.87±0.08 (n=449)	0.88±0.08 (n=125)	0.88±0.05 (n=13)	1.00 (0.26)
SBP (mm Hg)	130.57±17.52 (n=449)	131.34±19.15 (n=125)	131.77±21.30 (n=13)	0.95 (0.14)
DBP (mm Hg)	81.99±11.46 (n=448)	82.53±13.73 (n=125)	84.23±12.30 (n=13)	0.75 (0.07)
LogTG	0.23±0.53 (n=309)	0.19±0.62 (n=90)	0.39±0.62 (n=10)	0.50 (0.12)
TC (mmol/l)	5.47±0.90 (n=309)	5.52±1.00 (n=90)	5.09±1.01 (n=10)	0.26 (0.04)
HDL-C (mmol/l)	1.30±0.27 (n=309)	1.30±0.27 (n=90)	1.27±0.29 (n=10)	0.83 (0.16)
LDL-C (mmol/l)	3.50±0.80 (n=309)	3.59±0.88 (n=90)	3.04±0.87 (n=10)	0.10 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.24 Genetic effects of the FTO rs7191513 on obesity in Malaysian Malays

FTO rs7191513 SNP, is an intronic SNP. Table 4.26 shows the genetic influence of the FTO rs7191513 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards higher WHR and logTG and lower height compared to AG and AA carriers; the AA homozygotes showed trend towards higher weight, logBMI, WC, HC, SBP, DBP, TC, HDL-C and LDL-C compared to AG and GG carriers.

Table 4.26 : Genetic effects of the FTO rs7191513 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=273)	1.59±0.10 (n=249)	1.59±0.09 (n=65)	0.47 (0.51)
Weight(kg)	67.92±13.47 (n=273)	68.50±14.97 (n=249)	71.74±12.4 (n=65)	0.15 (0.08)
LogBMI	3.47±0.85 (n=273)	3.53±0.76 (n=249)	3.64±0.90 (n=65)	0.93 (0.03)
WC (cm)	89.02±11.12 (n=273)	89.18±13.02 (n=249)	90.79±10.11 (n=65)	0.53 (0.01)
HC (cm)	101.47±9.50 (n=273)	102.01±10.43 (n=249)	104.89±9.09 (n=65)	0.06 (0.03)
WHR	0.88±0.07 (n=273)	0.87±0.08 (n=249)	0.87±0.08 (n=65)	0.64 (0.26)
SBP (mm Hg)	130.46±17.76 (n=273)	130.11±17.41 (n=249)	130.71±17.93 (n=65)	0.74 (0.14)
DBP (mm Hg)	81.81±11.53 (n=273)	82.03±12.29 (n=249)	84.06±12.62 (n=65)	0.37 (0.06)
LogTG	0.26±0.54 (n=185)	0.20±0.58 (n=178)	0.20±0.50 (n=46)	0.67 (0.12)
TC (mmol/l)	5.45±0.97 (n=185)	5.47±0.85 (n=178)	5.59±1.02 (n=46)	0.63 (0.02)
HDL-C (mmol/l)	1.30±0.28 (n=185)	1.30±0.27 (n=178)	1.32±0.25 (n=46)	0.88 (0.17)
LDL-C (mmol/l)	3.47±0.85 (n=185)	3.53±0.76 (n=178)	3.64±0.90 (n=46)	0.42 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.25 Genetic effects of the FTO rs7204609 on obesity in Malaysian Malays

FTO rs7204609 SNP, is an intronic SNP. Table 4.27 shows the genetic influence of the FTO rs7204609 SNP on obesity parameters. There is a significant difference between TT compared to CT and CC groups, with TC after adjustment for age and gender. However, after Bonferroni correction ($\alpha=0.002$), no significant difference was found between TT compared to CT and CC groups with TC. The CC homozygotes showed trend towards lower WHR, LDL-C and TC levels compared to CT and TT carriers. The TT homozygotes showed trend towards higher height and weight and lower logBMI compared to CT and CC carriers; the CT heterozygotes showed trend towards higher HC, WC and logTG compared to TT and CC homozygotes; the CC homozygotes showed trend towards higher HDL-C, SBP and DBP compared to CT and TT carriers.

Table 4.27 : Genetic effects of the FTO rs7204609 on obesity parameters

Parameter	TT	CT	CC	p (R ²)
Height(m)	1.59±0.09 (n=263)	1.58±0.09 (n=251)	1.58±0.10 (n=73)	0.53 (0.51)
Weight(kg)	68.96±14.05 (n=263)	68.45±14.31 (n=251)	67.80±13.36 (n=73)	0.98 (0.08)
LogBMI	3.28±0.19 (n=263)	3.29±0.18 (n=251)	3.29±0.18 (n=73)	0.96 (0.02)
WC (cm)	89.46±11.69 (n=263)	89.72±12.16 (n=251)	87.36±11.39 (n=73)	0.47 (0.06)
HC (cm)	102.03±9.88 (n=263)	102.19±10.07 (n=251)	101.94±9.91 (n=73)	0.98 (0.02)
WHR	0.88±0.07 (n=263)	0.88±0.08 (n=251)	0.86±0.08 (n=73)	0.12 (0.26)
SBP (mm Hg)	130.28±18.31 (n=263)	130.44±17.03 (n=251)	133.23±19.65 (n=73)	0.61 (0.14)
DBP (mm Hg)	81.98±12.36 (n=263)	82.33±11.43 (n=251)	82.49±12.40 (n=73)	0.87 (0.06)
LogTG	0.22±0.58 (n=191)	0.25±0.55 (n=166)	0.14±0.47 (n=52)	0.25 (0.12)
TC (mmol/l)	5.49±0.97 (n=191)	5.54±0.87 (n=166)	5.19±0.89 (n=52)	0.04 (0.03)
HDL-C (mmol/l)	1.28±0.26 (n=191)	1.31±0.27 (n=166)	1.35±0.30 (n=52)	0.59 (0.17)
LDL-C (mmol/l)	3.55±0.83 (n=191)	3.55±0.81 (n=166)	3.26±0.77 (n=52)	0.06 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.26 Genetic effects of the FTO rs7206790 on obesity in Malaysian Malays

FTO rs7206790 SNP, is an intronic SNP. Table 4.28 shows the genetic influence of the FTO rs7206790 SNP on obesity parameters. There is no significant difference among the subjects having CC, CG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The CG heterozygotes showed trend towards higher WHR, SBP, DBP, logTG, TC and HDL-C compared to CC and GG homozygotes; the GG homozygotes showed trend towards higher height, weight, logBMI, WC, HC and LDL-C compared to CC and CG carriers.

Table 4.28 : Genetic effects of the FTO rs7206790 on obesity parameters

Parameter	CC	CG	GG	p (R ²)
Height(m)	1.58±0.10 (n=293)	1.58±0.09 (n=241)	1.60±0.08 (n=53)	0.38 (0.51)
Weight(kg)	68.24±14.33 (n=293)	68.69±13.93 (n=241)	70.05±13.12 (n=53)	0.77 (0.08)
LogBMI	3.28±0.19 (n=293)	3.29±0.18 (n=241)	3.30±0.18 (n=53)	0.60 (0.03)
WC (cm)	88.68±11.85 (n=293)	89.87±12.04 (n=241)	90.00±11.03 (n=53)	0.65 (0.00)
HC (cm)	102.11±9.98 (n=293)	101.76±9.77 (n=241)	103.39±10.12 (n=53)	0.31 (0.03)
WHR	0.87±0.08 (n=293)	0.88±0.08 (n=241)	0.87±0.08 (n=53)	0.04 (0.26)
SBP (mm Hg)	130.10±19.41 (n=293)	130.40±16.22 (n=241)	129.98±17.07 (n=53)	0.76 (0.14)
DBP (mm Hg)	82.14±12.57 (n=293)	82.43±11.38 (n=241)	80.96±11.41 (n=53)	0.59 (0.06)
LogTG	0.22±0.55 (n=198)	0.23±0.56 (n=176)	0.19±0.52 (n=35)	0.82 (0.13)
TC (mmol/l)	5.42±0.96 (n=198)	5.53±0.91 (n=176)	5.48±0.77 (n=35)	0.38 (0.02)
HDL-C (mmol/l)	1.30±0.28 (n=198)	1.31±0.27 (n=176)	1.25±0.25 (n=35)	0.60 (0.17)
LDL-C (mmol/l)	3.45±0.86 (n=198)	3.56±0.79 (n=176)	3.60±0.73 (n=35)	0.34 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.27 Genetic effects of the FTO rs8050136 on obesity in Malaysian Malays

FTO rs8050136 SNP, is an intronic SNP. Table 4.29 shows the genetic influence of the FTO rs8050136 SNP on obesity parameters. There is no significant difference among the subjects having CC, CA and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The CA heterozygotes showed trend towards higher HDL-C and lower DBP compared to CC and AA homozygotes; the AA homozygotes showed trend towards higher height, weight, logBMI, WC, HC, LDL-C, TC, logTG and SBP compared to CC and CA carriers; the CC homozygotes showed trend towards lower WHR compared to CA and AA carriers.

Table 4.29 : Genetic effects of the FTO rs8050136 on obesity parameters

Parameter	CC	CA	AA	p (R ²)
Height(m)	1.59±0.09 (n=287)	1.58±0.09 (n=240)	1.60±0.08 (n=60)	0.38 (0.51)
Weight(kg)	68.38±14.33 (n=287)	68.03±13.39 (n=240)	71.76±15.01 (n=60)	0.51 (0.09)
LogBMI	3.29±0.18 (n=287)	3.29±0.18 (n=240)	3.31±0.19 (n=60)	0.44 (0.03)
WC (cm)	88.87±12.17 (n=287)	89.33±11.57 (n=240)	91.11±11.47 (n=60)	0.54 (0.07)
HC (cm)	101.95±9.94 (n=287)	101.97±9.72 (n=240)	103.17±10.51 (n=60)	0.43 (0.03)
WHR	0.87±0.08 (n=287)	0.88±0.07 (n=240)	0.88±0.07 (n=60)	0.57 (0.26)
SBP (mm Hg)	131.27±18.78 (n=287)	129.43±17.25 (n=240)	133.10±16.19 (n=60)	0.48 (0.14)
DBP (mm Hg)	82.17±12.04 (n=287)	82.14±11.96 (n=240)	82.17±12.96 (n=60)	0.95 (0.06)
LogTG	0.22±0.56 (n=192)	0.22±0.55 (n=171)	0.23±0.55 (n=46)	0.95 (0.12)
TC (mmol/l)	5.40±0.91 (n=192)	5.50±0.90 (n=171)	5.67±1.06 (n=46)	0.09 (0.05)
HDL-C (mmol/l)	1.30±0.28 (n=192)	1.31±0.26 (n=171)	1.27±0.30 (n=46)	0.95 (0.16)
LDL-C (mmol/l)	3.44±0.80 (n=192)	3.54±0.83 (n=171)	3.71±0.87 (n=46)	0.06 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.28 Genetic effects of the FTO rs9935401 on obesity in Malaysian Malays

FTO rs9935401 SNP, is an intronic SNP. Table 4.30 shows the genetic influence of the FTO rs9935401 SNP on obesity parameters. There is no significant difference among the subjects having GG, GA and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards higher HC compared to GA and AA; the GA heterozygotes showed trend towards higher DBP and HDL-C compared to GG and AA carriers; the AA homozygotes showed trend towards higher height, weight, logBMI, WC, LDL-C, TC, logTG and SBP compared to GG and GA carriers; the GG homozygotes showed trend towards lower WHR compared to GA and AA carriers.

Table 4.30 : Genetic effects of the FTO rs9935401 on obesity parameters

Parameter	GG	GA	AA	p (R ²)
Height(m)	1.58±0.09 (n=287)	1.58±0.09(n=240)	1.60±0.08 (n=60)	0.39 (0.51)
Weight(kg)	68.34±14.35 (n=287)	67.99±13.31 (n=240)	72.15±15.06 (n=60)	0.13 (0.09)
LogBMI	3.29±0.18 (n=287)	3.29±0.18 (n=240)	3.31±0.20 (n=60)	0.31 (0.03)
WC (cm)	88.80±12.22 (n=287)	89.35±11.53 (n=240)	91.56±11.30 (n=60)	0.44 (0.07)
HC (cm)	101.98±9.94 (n=287)	101.85±9.60 (n=240)	101.85±9.60 (n=60)	0.27 (0.03)
WHR	0.87±0.08 (n=287)	0.88±0.07 (n=240)	0.88±0.07 (n=60)	0.51 (0.26)
SBP (mm Hg)	131.14±18.84 (n=287)	129.60±17.18 (n=240)	133.07±16.22 (n=60)	0.52 (0.14)
DBP (mm Hg)	82.14±12.06 (n=287)	82.17±11.94 (n=239)	82.15±12.98 (n=60)	0.97 (0.06)
LogTG	0.23±0.56 (n=189)	0.22±0.56 (n=173)	0.24±0.55 (n=47)	1.00 (0.12)
TC (mmol/l)	5.40±0.91 (n=189)	5.50±0.90 (n=173)	5.65±1.06 (n=47)	0.12 (0.05)
HDL-C (mmol/l)	1.30±0.28 (n=189)	1.31±0.26 (n=173)	1.27±0.30 (n=47)	0.90 (0.16)
LDL-C (mmol/l)	3.43±0.80 (n=189)	3.55±0.82 (n=173)	3.69±0.87 (n=47)	0.09 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.29 Genetic effects of the FTO rs9939609 on obesity in Malaysian Malays

FTO rs9939609 SNP, is an intronic SNP. Table 4.31 shows the genetic influence of the FTO rs9939609 SNP on obesity parameters. There is no significant difference among the subjects having TT, TA and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The TA heterozygotes showed trend towards higher DBP and HDL-C compared to TT and AA carriers; AA homozygotes showed trend towards higher height, weight, logBMI, WC, HC, LDL-C, TC, logTG and SBP compared to TT and TA carriers; the TT homozygotes showed trend towards lower WHR compared to TA and AA carriers.

Table 4.31 : Genetic effects of the FTO rs9939609 on obesity parameters

Parameter	TT	TA	AA	p (R ²)
Height(m)	1.58±0.09 (n=287)	1.58±0.09(n=240)	1.60±0.08 (n=60)	0.36 (0.51)
Weight(kg)	68.35±14.33 (n=287)	67.97±13.34 (n=240)	72.15±15.06 (n=60)	0.12 (0.09)
LogBMI	3.29±0.18 (n=287)	3.29±0.18 (n=240)	3.31±0.20 (n=60)	0.31 (0.03)
WC (cm)	88.84±12.21 (n=287)	89.31±11.54 (n=240)	91.36±11.30 (n=60)	0.46 (0.07)
HC (cm)	101.99±9.92 (n=287)	101.83±9.62 (n=240)	103.49±10.88 (n=60)	0.27 (0.03)
WHR	0.87±0.08 (n=287)	0.88±0.07 (n=240)	0.88±0.07 (n=60)	0.57 (0.26)
SBP (mm Hg)	131.14±18.84 (n=287)	129.60±17.18 (n=240)	133.07±16.22 (n=60)	0.52 (0.14)
DBP (mm Hg)	82.14±12.06 (n=287)	82.17±11.94 (n=239)	82.15±12.98 (n=60)	0.95 (0.06)
LogTG	0.23±0.56 (n=189)	0.22±0.56 (n=173)	0.24±0.55 (n=47)	0.97 (0.12)
TC (mmol/l)	5.40±0.91 (n=189)	5.50±0.90 (n=173)	5.65±1.06 (n=47)	0.13 (0.05)
HDL-C (mmol/l)	1.30±0.28 (n=189)	1.31±0.26 (n=173)	1.27±0.30 (n=47)	0.86 (0.16)
LDL-C (mmol/l)	3.44±0.80 (n=189)	3.55±0.82 (n=173)	3.69±0.87 (n=47)	0.09 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.30 Genetic effects of the FTO rs9939973 on obesity in Malaysian Malays

FTO rs9939973 SNP, is an intronic SNP. Table 4.32 shows the genetic influence of the FTO rs9939973 SNP on obesity parameters. There is a significant difference between GG compared to GA and AA groups, with LDL-C after adjustment for age and gender. However, after Bonferroni correction ($\alpha=0.002$), no significant difference was found between GG compared to GA and AA groups with LDL-C. The GG homozygotes showed trend towards higher logTG and lower WHR compared to GA and AA carriers; GA heterozygotes showed trend towards higher HC and DBP compared to GG and AA homozygotes; the AA homozygotes showed trend towards higher height, weight, WC, LDL-C, TC and SBP and lower LDL-C compared to GG and GA carriers.

Table 4.32 : Genetic effects of the FTO rs9939973 on obesity parameters

Parameter	GG	GA	AA	p (R ²)
Height(m)	1.59±0.09 (n=271)	1.58±0.09 (n=243)	1.59±0.09 (n=73)	0.70 (0.51)
Weight(kg)	68.49±14.25 (n=271)	68.51±13.20 (n=243)	69.23±16.04 (n=73)	0.93 (0.08)
LogBMI	3.29±0.18 (n=271)	3.29±0.18 (n=243)	3.29±0.21 (n=73)	0.97 (0.03)
WC (cm)	88.87±12.17 (n=271)	89.64±11.42 (n=243)	89.66±12.17 (n=73)	0.82 (0.07)
HC (cm)	102.04±9.78 (n=271)	102.12±9.50 (n=243)	102.11±11.61 (n=73)	0.98 (0.03)
WHR	0.87±0.08 (n=271)	0.88±0.08 (n=243)	0.88±0.07 (n=73)	0.47 (0.26)
SBP (mm Hg)	131.07±19.05 (n=271)	129.69±16.77 (n=243)	132.75±18.08 (n=73)	0.54 (0.14)
DBP (mm Hg)	82.08±12.10 (n=271)	82.29±11.70 (n=243)	82.00±12.61 (n=73)	0.92 (0.06)
LogTG	0.23±0.56 (n=183)	0.22±0.55 (n=173)	0.21±0.55 (n=52)	0.89 (0.12)
TC (mmol/l)	5.38±0.91 (n=183)	5.51±0.89 (n=173)	5.66±1.07 (n=52)	0.10 (0.05)
HDL-C (mmol/l)	1.30±0.29 (n=183)	1.30±0.25 (n=173)	1.28±0.30 (n=52)	0.97 (0.16)
LDL-C (mmol/l)	3.42±0.79 (n=183)	3.55±0.82 (n=173)	3.71±0.89 (n=52)	0.04 (0.04)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.1.31 LD and haplotype analysis of FTO gene

The data from thirty FTO SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.1 shows the haplotype block and LD pattern of FTO gene. D prime value (D') of 1.0 shows the strong linkage disequilibrium. D' values of 1.0 are not shown (the box is empty). The boxes in bright red are with D' values of 1.0. The boxes with values of D'<1.0 are in shades of pink or red. There were two haplotype

blocks of 1 kb and 44 kb respectively in the FTO region. The first block contains of FTO rs11643744 and rs7186521 SNPs while the second block contains of the FTO rs9939609 SNP, the SNP which highly reported to be the core variant associated with obesity and many other FTO SNPs.

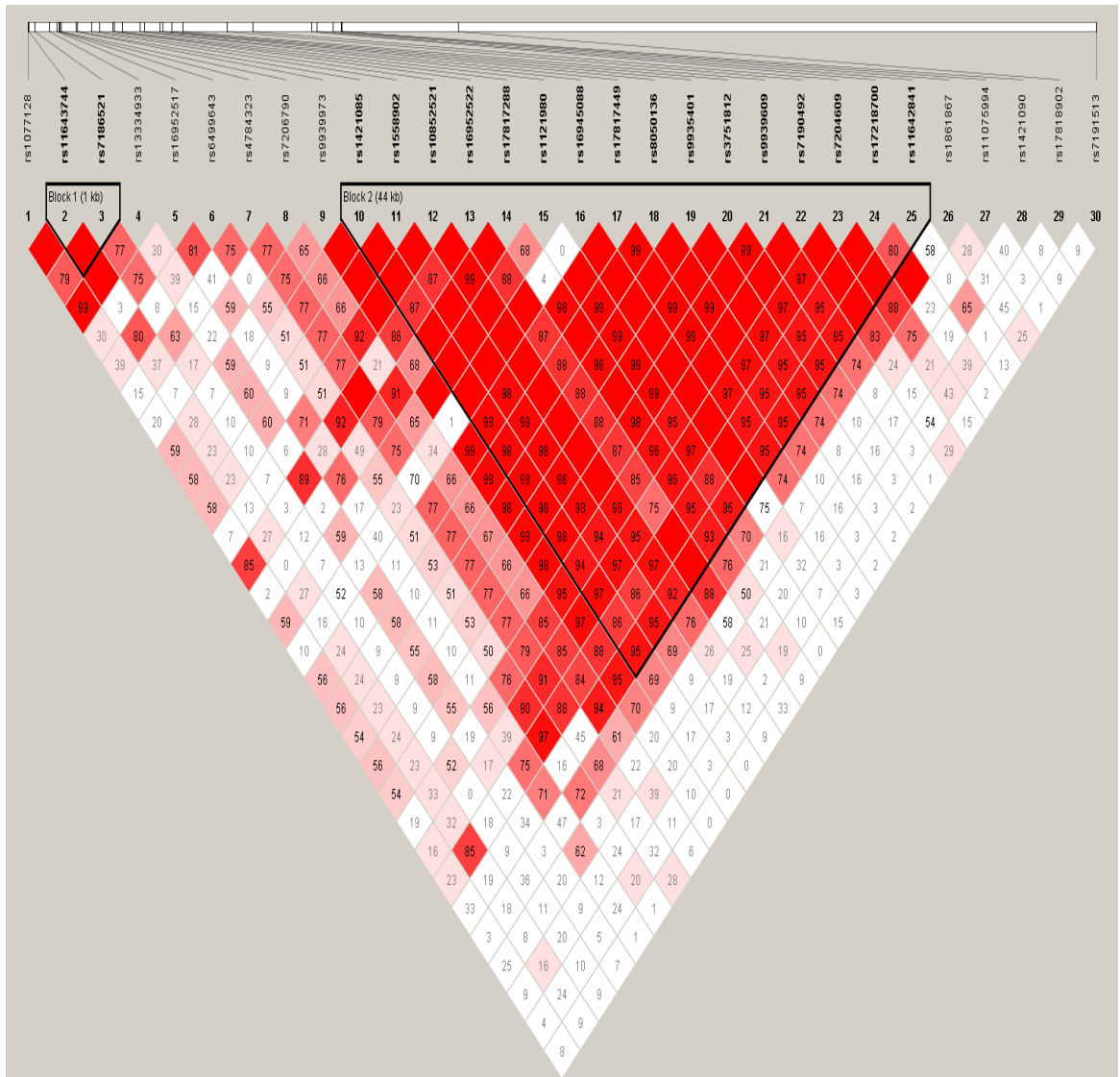


Figure 4.1 : Haplotype block of FTO gene of non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 30 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

The strongest LD was seen in the second block that showed 48 pairs with complete LD and 69 pairs with high LD ($D' = 80-99\%$). In total, 57 regions were in complete LD ($D' = 1.0$) in this haplotype block. Complete LD was observed at FTO rs10852521 SNP with FTO rs16945088, rs17817449, rs9939673, rs1421085,

rs1558902, rs16952522, rs3751812, rs8050136, rs9935401, rs9939609 and rs1121980 SNPs. Complete LD was observed at FTO rs1121980 SNP with FTO rs1421085, rs1558902, rs17817449 and rs9939973 SNPs. Complete LD was observed at FTO rs11642841 with rs7204609, rs16945088, rs16952522 and rs7190492 SNPs. Complete LD was observed at FTO rs11643744 SNP with FTO rs1077128, rs7186521 and rs13334933 SNPs. Complete LD was observed at FTO rs1421085 SNP with FTO rs17817288, rs16945088, rs1558902 and rs9939973 SNPs. Complete LD was observed at FTO rs1558902 SNP with FTO rs17817288, rs16945088 and rs9939973 SNPs. Complete LD was observed at FTO rs16945088 SNP with FTO rs16952522, rs3751812, rs7204609, rs8050136, rs9935401 and rs9939609 SNPs. Complete LD was observed at FTO rs16952522 SNP with FTO rs17817288 SNP, FTO rs17817449 SNP with FTO rs16952522 SNP and FTO rs17218700 SNP with FTO rs7190492, rs7204609, rs16945088 and rs16952522 SNPs. Complete LD was observed at FTO rs17817288 SNP with FTO rs3751812 and rs8050136 SNPs, FTO rs17817449 SNP with FTO rs16945088, rs7190492, rs9935401 and rs9939609 SNPs, FTO rs3751812 SNP with FTO rs9935401, rs7190492 and rs8050136 SNPs, FTO rs4784323 SNP with FTO rs16952522 SNP, FTO rs7190492 SNP with FTO rs7204609, rs8050136, rs9935401, rs9939609 SNPs and FTO rs9935401 SNP with FTO rs8050136 and rs9939609 SNPs.

LD analysis was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.2 shows the haplotype block and LD pattern of FTO gene in non-obese and obese participants. It was observed that the LD pattern of FTO gene in the non-obese participants is similar to that of the non-obese and obese participants.

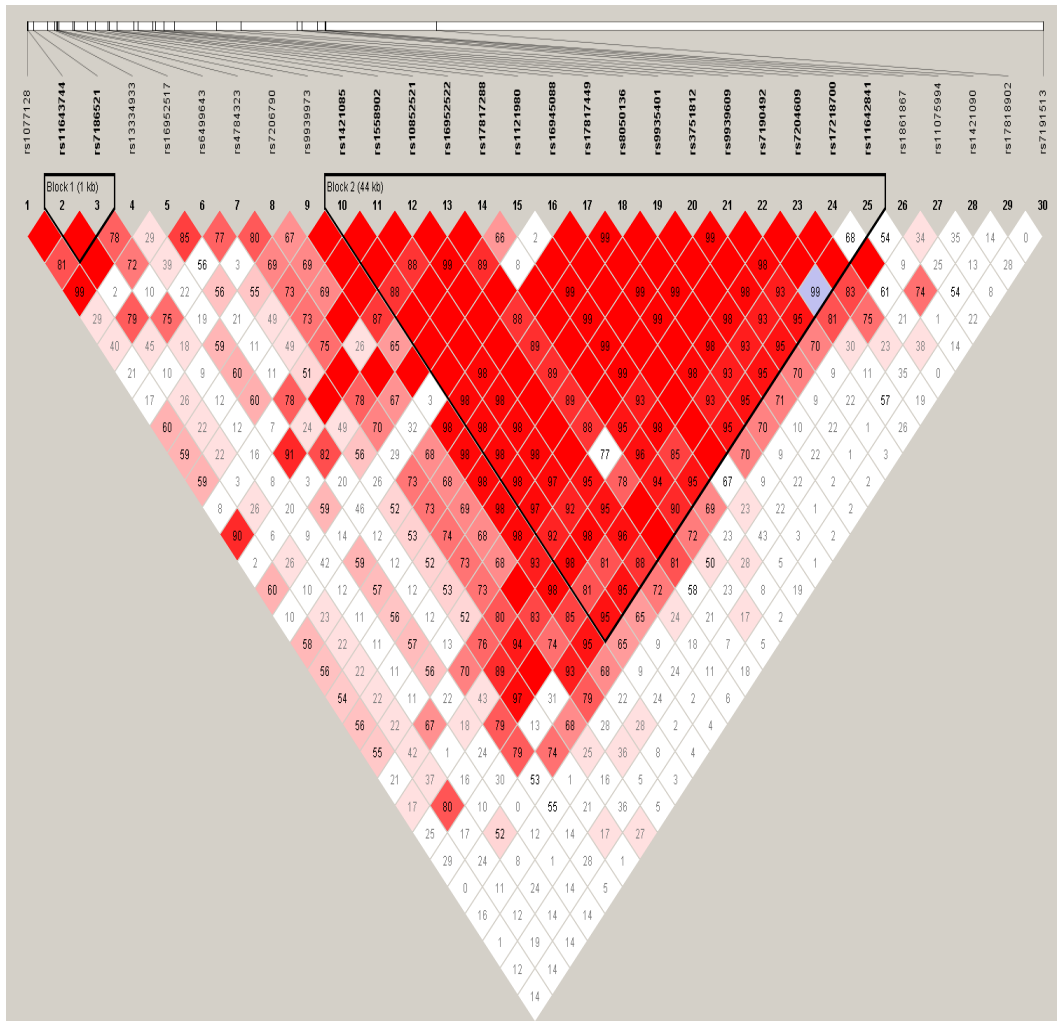


Figure 4.2 : Haplotype block of FTO gene of non-obese participants

*The figure shows the linkage disequilibrium pattern among 30 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

There are 11 haplotypes found in the chromosomal region of the FTO gene. Nine FTO haplotypes had high frequencies (more than 5%) while two FTO haplotypes had low frequencies (less than 5%). FTO haplotype GA had higher haplotype frequency (0.36) while CACCGTAGAATAGTGC haplotype had lower haplotype frequency (0.02). The FTO haplotypes were tested for association with obesity. Table 4.33 shows the block 1 and block 2 of the FTO haplotypes. The GA, AA and AG haplotypes in the block 1 showed frequencies of 36%, 33% and 32% respectively. In the block 2, the TTCCGCATCGGTGCGC, CACCGTAGAATAGTGA, CACGGTAGAATAGTGC, TTTCACATCGGTGTAC, TTTCACATCGGTATGC, TTCCGCGTCGGTGTGC and

TTCCGCGTCGGTGTGC haplotypes in the block 2 had frequencies of 32%, 14%, 14%, 13%, 12% and 5% respectively. The TTCCATGTCGGTGTGC and CACCGTAGAATAGTGC haplotypes had lower frequencies (<5%). There was no significant difference in haplotype frequencies between obese and non-obese group. After correcting for permutation testing with 5000 permutations, none of the haplotypes were associated with obesity.

Table 4.33 : Association analysis of FTO haplotype

Block	Freq.	Non-obese Freq	Obese Freq	χ^2	p
Block 1					
GA	0.36	0.37	0.35	0.43	1.00
AA	0.33	0.31	0.33	0.25	1.00
AG	0.32	0.32	0.32	0.03	1.00
Block 2					
TTCCGCATCGGTGCGC	0.32	0.33	0.32	0.03	1.00
CACCGTAGAATAGTGA	0.14	0.13	0.14	0.36	1.00
CACGGTAGAATAGTGC	0.14	0.15	0.13	0.63	1.00
TTTCACATCGGTGTAC	0.13	0.11	0.14	1.09	1.00
TTTCACATCGGTATGC	0.12	0.13	0.12	0.34	1.00
TTCCGCGTCGGTGTGC	0.05	0.05	0.05	0.00	1.00
TTCCATGTCGGTGTGC	0.03	0.03	0.03	0.15	1.00
CACCGTAGAATAGTGC	0.02	0.03	0.02	0.29	1.00

*p-values were determined using chi-square after correcting for 5000 permutations.

4.3.2 Genetic profiling of melanocortin-4 receptor gene (MC4R)

A total of five MC4R SNPs were genotyped in this study. Table 4.34 summarizes the allele frequencies in the obese and non-obese subjects of the MC4R SNPs. Five-thousand permutation test were performed to analyze the individual SNPs. The marker chromosome position, minor allele frequencies (MAF) and allele frequencies in the obese and non-obese subjects of the 3 SNPs studied in the MC4R are summarized in Table 4.34. The following MC4R SNPs did not deviate from the Hardy-Weinberg equilibrium: MC4R rs571312, rs2229616 and rs7227255 SNPs. However, MC4R rs1295734 SNP (p HWE case: control=0.91/0.03) and MC4R rs17700144 SNP (p HWE case: control=0.60/0.03) deviated from the Hardy-Weinberg equilibrium. Therefore, MC4R rs1295734 and rs17700144 SNPs were removed from further analysis. After 5000 permutation test, no significant difference was found in the allelic frequency of each of the MC4R SNPs between the obese and non-obese group.

Table 4.34 : Allelic distribution of MC4R SNPs among obese and non-obese groups

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	p	HWE (P ^a /P ^b)
rs571312	57839769	0.13	T	0.14	0.13	0.09	0.98	0.15/0.32
rs2229616	58039276	0.03	G	0.98	0.98	0.01	1.00	0.75/0.58
rs7227255	58055731	0.01	A	0.02	0.01	1.08	0.65	0.85/0.85

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- p value for HWE in obese/ p value for HWE in non-obese

*p-values were determined using chi-square test with 5000 permutation test

4.3.2.1 Genetic effects of the MC4R rs571312 on obesity in Malaysian Malays

MC4R rs571312 SNP is observed to be linked with obesity traits in the Malaysian Malays. Table 4.35 shows the genetic influence of the MC4R rs571312 SNP on obesity parameters. There were significant differences between GG compared to GT and TT groups, with logBMI and SBP after the Bonforreni correction ($\alpha=0.017$) and adjustment for age and gender. The TT homozygotes had significantly lower logBMI and higher SBP compared to GG and GT carriers. The TT homozygotes showed trend towards higher DBP compared to GT and GG carriers. The TT homozygotes showed trend towards lower height, weight, WC, HC, WHR, logTG, TC, HDL-C and LDL-C compared to GT and GG carriers.

Table 4.35 : Genetic effects of the MC4R rs571312 on obesity parameters

	GG	GT	TT	p (R ²)
Height(m)	1.59±0.09 (n=489)	1.58±0.08 (n=151)	1.57±0.09 (n=12)	0.26 (0.52)
Weight(kg)	68.07±13.83 (n=489)	70.33±13.66 (n=151)	62.47±19.44 (n=12)	0.10 (0.09)
LogBMI	3.28±0.18 (n=489)	3.33±0.16 (n=151)	3.19±0.22 (n=12)	0.008* (0.04)
WC (cm)	89.01±11.86 (n=489)	90.28±10.60 (n=151)	84.21±17.60 (n=12)	0.13 (0.06)
HC (cm)	101.94±9.76 (n=489)	102.84±9.63 (n=151)	97.04±14.77 (n=12)	0.29 (0.03)
WHR	0.87±0.08 (n=489)	0.88±0.08 (n=151)	0.86±0.06 (n=12)	0.08 (0.25)
SBP (mm Hg)	130.19±18.14 (n=489)	131.12±17.06 (n=151)	145.67±36.50 (n=12)	0.005* (0.13)
DBP (mm Hg)	81.81±12.17 (n=489)	82.90±11.41 (n=151)	85.08±16.66 (n=12)	0.19 (0.05)
LogTG	0.22±0.56 (n=346)	0.29±0.55 (n=100)	0.02±0.73 (n=10)	0.10 (0.14)
TC (mmol/l)	5.49±0.94 (n=346)	5.49±1.00 (n=100)	5.22±0.84 (n=10)	0.63 (0.03)
HDL-C (mmol/l)	1.30±0.28 (n=346)	1.31±0.26 (n=100)	1.28±0.20 (n=10)	0.96 (0.16)
LDL-C (mmol/l)	3.53±0.83 (n=346)	3.50±0.88 (n=100)	3.37±0.70 (n=10)	0.77 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.2.2 Genetic effects of the MC4R rs7227255 on obesity in Malaysian Malays

MC4R rs7227255 SNP had no effect on obesity traits in the Malaysian Malays. Table 4.36 shows the genetic influence of the MC4R rs7227255 SNP on obesity parameters. There is no significant difference among the subjects having GG and AG in all the obesity and obesity-related parameters after adjustment for age and gender. The AG heterozygotes showed trend towards lower logTG, TC, HDL-C and LDL-C compared to GG homozygotes. The AG carriers showed trend towards higher height, weight, logBMI, WC, HC, WHR, SBP and DBP compared GG homozygotes.

Table 4.36 : Genetic effects of the MC4R rs7227255 on obesity parameters

Parameter	GG	AG	AA	P (R ²)
Height(m)	1.59±0.09 (n=639)	1.60±0.11 (n=13)	0	0.86 (0.51)
Weight(kg)	68.37±13.93 (n=639)	73.98±14.02 (n=13)	0	0.22 (0.01)
LogBMI	3.28±0.18 (n=639)	3.35±0.16 (n=13)	0	0.15 (0.03)
WC (cm)	89.14±11.73 (n=639)	92.38±11.67 (n=13)	0	0.38 (0.05)
HC (cm)	102.01±9.87 (n=639)	104.15±9.25 (n=13)	0	0.41 (0.02)
WHR	0.87±0.08 (n=639)	0.89±0.10 (n=13)	0	0.64 (0.24)
SBP (mm Hg)	130.60±18.26 (n=639)	135.23±27.19 (n=13)	0	0.34 (0.12)
DBP (mm Hg)	82.09±11.96 (n=639)	83.51±17.94 (n=13)	0	0.75 (0.05)
LogTG	0.23±0.56 (n=443)	0.13±0.59 (n=13)	0	0.42 (0.13)
TC (mmol/l)	5.50±0.94 (n=443)	5.17±1.11 (n=13)	0	0.19 (0.02)
HDL-C (mmol/l)	1.30±0.27 (n=443)	1.18±0.23 (n=13)	0	0.10 (0.16)
LDL-C (mmol/l)	3.53±0.83 (n=443)	3.38±0.98 (n=13)	0	0.51 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.2.3 Genetic effects of the MC4R rs2229616 on obesity in Malaysian Malays

MC4R rs2229616 SNP, is a missense SNP. Table 4.37 shows the genetic influence of the MC4R rs2229616 SNP on obesity parameters. There is a significant difference between GG compared to GA group, with TC level after Bonferroni correction ($\alpha=0.017$) and adjustment for age and gender. The GA heterozygotes had significantly lower TC level compared to GG homozygotes. The GA heterozygotes showed trend towards higher weight, logBMI, WC and HC and lower height, DBP, SBP, HDL-C, LDL-C and logTG compared to GG carriers.

Table 4.37 : Genetic effects of the MC4R rs2229616 on obesity parameters

Parameter	GG	GA	AA	p (R ²)
Height(m)	1.59±0.09 (n=620)	1.57±0.10 (n=32)	0	0.07 (0.51)
Weight(kg)	68.41±13.89 (n=620)	69.89±15.12 (n=32)	0	0.65 (0.08)
LogBMI	3.28±0.18 (n=620)	3.32±0.17 (n=32)	0	0.22 (0.03)
WC (cm)	89.17±11.68 (n=620)	89.90±12.75 (n=32)	0	0.61 (0.05)
HC (cm)	102.02±9.89 (n=620)	102.83±9.34 (n=32)	0	0.68 (0.02)
WHR	0.87±0.08 (n=620)	0.87±0.09 (n=32)	0	0.84 (0.24)
SBP (mm Hg)	130.70±18.11 (n=620)	130.63±25.02 (n=32)	0	0.71 (0.12)
DBP (mm Hg)	82.18±12.00 (n=620)	80.93±13.87 (n=32)	0	0.73 (0.05)
LogTG	0.23±0.57 (n=437)	0.11±0.53 (n=19)	0	0.27 (0.13)
TC (mmol/l)	5.51±0.95 (n=437)	4.98±0.86 (n=19)	0	0.016* (0.03)
HDL-C (mmol/l)	1.30±0.27 (n=437)	1.23±0.27 (n=19)	0	0.31 (0.16)
LDL-C (mmol/l)	3.54±0.84 (n=437)	3.17±0.70 (n=19)	0	0.06 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.2.4 LD and haplotype analysis of MC4R gene

The data from three MC4R SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.3 shows the haplotype block and LD pattern of MC4R gene. D prime value (D') of 1.0 shows the complete linkage disequilibrium. The boxes in bright red are with D' values of 1.0. The boxes in red are with strong LD. The boxes with values of D' <1.0 are in shades of pink or red. Low LD were observed at MC4R rs571312 SNP with MC4R rs2229616 (D'=0.05) and rs7227255 (D'=0.33) SNPs.

Low LD was observed at MC4R rs2229616 SNP with MC4R rs7227255 SNP ($D'=0.67$).

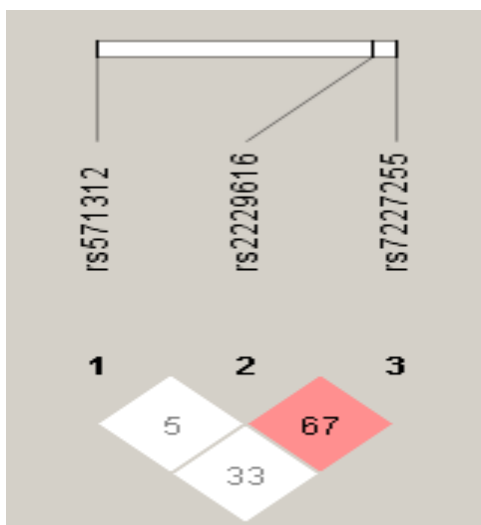


Figure 4.3 : LD pattern of MC4R gene in non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 3 selected SNPs. White denotes a non-significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

LD analysis was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.4 shows the haplotype block and LD pattern of MC4R gene in non-obese and obese participants. It was observed that the LD pattern of MC4R gene in the non-obese participants is slightly different to that of the non-obese and obese subjects.

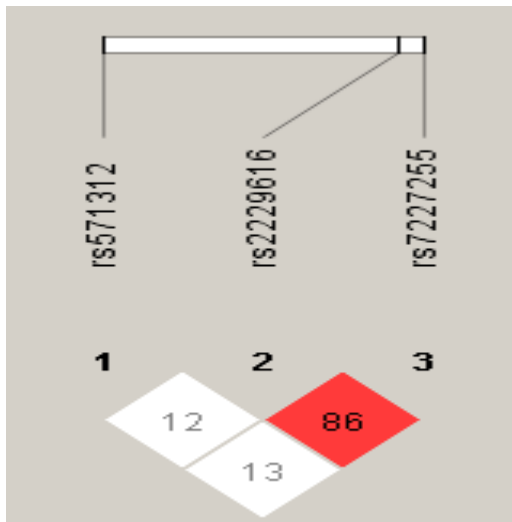


Figure 4.4 : LD pattern of MC4R gene in non-obese participants

*The figure shows the linkage disequilibrium pattern among 3 selected SNPs. Red denotes a non-significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

The MC4R haplotypes were tested for association with obesity. A haplotype block found in the MC4R gene region in this study. There are 3 haplotypes found in the chromosomal region of the MC4R gene. Two MC4R haplotypes had high frequencies (more than 5%) while a haplotypes had low frequencies (less than 5%). MC4R haplotype GGG had higher haplotype frequency (0.84) and GAG haplotype had lower haplotype frequency (0.02).

Table 4.38 shows the block 1 of the MC4R haplotypes. The GGG, TGG and GAG haplotypes in the block 1 showed frequencies of 84%, 13% and 32% respectively. The GAG haplotypes had lower frequencies (<5%). There was no significant difference in haplotype frequencies between obese and non-obese group. After correcting for permutation testing with 5000 permutations, none of the haplotypes were associated with obesity.

Table 4.38 : Association analysis of MC4R haplotype

Block	Freq.	Obese Freq	Non-Obese Freq	χ^2	p
Block 1					
GGG	0.84	0.83	0.85	0.52	0.89
TGG	0.13	0.14	0.13	0.22	0.97
GAG	0.02	0.02	0.01	0.29	0.95

**p*-values were determined using chi-square after correcting for 5000 permutations.

4.3.3 Genetic profiling of β_2 -adrenoceptor gene (ADRB2)

A total of five ADRB2 SNPs were genotyped in this study. Table 4.39 summarizes the allele frequencies in the obese and non-obese subjects of the ADRB2 SNPs. Five-thousand permutation test was performed to analyze the individual SNPs. The marker chromosome position, minor allele frequencies (MAF) and allele frequencies in the obese and non-obese subjects of the 5 SNPs studied in the ADRB2 are summarized in Table 4.39. Following ADRB2 rs1042713, rs1042714, rs1042717, rs1042718 and rs1042719 SNPs did not deviate from the Hardy-Weinberg equilibrium. After 5000 permutation test, no significant was found difference in allelic frequency of each of the ADRB2 SNPs between the obese and non-obese group. Similar MAF was observed in ADRB2 rs1042713 and ADRB2 rs1042719 (0.45); ADRB2 rs1042717 and ADRB2 rs1042718 (0.44). The ADRB2 rs1042714 SNP had the lowest MAF (0.08).

Table 4.39 : Allelic distribution of ADRB2 SNPs among obese and non-obese groups

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	<i>p</i>	HWE (P ^a /P ^b)
rs1042713	148206440	0.45	G	0.56	0.55	0.05	1.00	0.21/0.51
rs1042714	148206473	0.08	C	0.92	0.92	0.12	1.00	0.28/0.11
rs1042717	148206646	0.44	A	0.45	0.43	0.30	0.96	0.37/0.39
rs1042718	148206917	0.44	A	0.45	0.43	0.13	0.99	0.75/0.50
rs1042719	148207447	0.45	C	0.58	0.54	1.36	0.61	0.86/0.09

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test with 5000 permutation test

4.3.3.1 Genetic effects of the ADRB2 rs1042713 on obesity in Malaysian Malays

ADRB2 rs1042713 SNP, is a missense SNP. Table 4.40 shows the genetic influence of the ADRB2 rs1042713 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards higher logTG and HDL-C compared to AG and GG carriers. The AA homozygotes showed trend towards lower logBMI, weight, HC and SBP compared to GG and GA carriers; the AG carriers showed trend towards higher WHR and LDL-C compared to GG and AA homozygotes; the GG homozygotes showed trend towards lower height and TC compared to AG and AA carriers.

Table 4.40 : Genetic effects of the ADRB2 rs1042713 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.10 (n=195)	1.59±0.09 (n=347)	1.59±0.09 (n=128)	0.57 (0.51)
Weight(kg)	68.22±13.76 (n=195)	68.62±14.57 (n=347)	67.64±13.07 (n=128)	0.69 (0.07)
LogBMI	3.29±0.18 (n=195)	3.28±0.19 (n=347)	3.27±0.18 (n=128)	0.67 (0.02)
WC (cm)	88.54±11.82 (n=195)	89.31±12.08 (n=347)	88.69±10.99 (n=128)	0.95 (0.06)
HC (cm)	102.19±9.54 (n=195)	101.88±10.34 (n=347)	101.67±9.33 (n=128)	0.88 (0.02)
WHR	0.87±0.08 (n=195)	0.88±0.08 (n=347)	0.87±0.07 (n=128)	0.76 (0.25)
SBP (mm Hg)	129.80±17.84 (n=195)	131.22±18.74 (n=347)	129.67±18.45 (n=128)	0.77 (0.12)
DBP (mm Hg)	81.23±13.32 (n=195)	82.47±12.11 (n=347)	82.22±11.55 (n=128)	0.62 (0.06)
LogTG	0.21±0.57 (n=133)	0.23±0.54 (n=244)	0.24±0.60 (n=86)	0.93 (0.13)
TC (mmol/l)	5.40±0.92 (n=133)	5.52±0.91 (n=244)	5.52±1.09 (n=86)	0.47 (0.03)
HDL-C (mmol/l)	1.30±0.25 (n=133)	1.29±0.27 (n=244)	1.32±0.29 (n=86)	0.55 (0.16)
LDL-C (mmol/l)	3.44±0.84 (n=133)	3.57±0.81 (n=244)	3.52±0.92 (n=86)	0.43 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.3.2 Genetic effects of the ADRB2 rs1042714 on obesity in Malaysian Malays

ADRB2 rs1042714 is a missense SNP. Table 4.41 shows the genetic influence of the ADRB2 rs1042714 SNP on obesity parameters. There is a significant difference between GG compared to GC and CC groups, with DBP after Bonferroni correction ($\alpha=0.01$) and adjustment for age and gender. The CC homozygotes had significantly higher DBP compared to GC and GG carriers after adjusted with age and gender. The CC homozygotes showed trend towards higher weight, logBMI, HC, WC, SBP, WHR and DBP compared to GC and GG carriers. The CC homozygotes showed trend towards lower TC and LDL-C levels compared to GC and GG carriers. The GC heterozygotes showed trend towards higher HDL-C and lower logTG and height compared to CC and GG homozygotes.

Table 4.41 : Genetic effects of the ADRB2 rs1042714 on obesity parameters

Parameter	GG	GC	CC	p (R ²)
Height(m)	1.62±0.10 (n=6)	1.58±0.09 (n=95)	1.59±0.09 (n=571)	0.63 (0.51)
Weight(kg)	65.13±7.01 (n=6)	67.02±13.60 (n=95)	68.55±14.18 (n=571)	0.42 (0.08)
LogBMI	3.20±0.09 (n=6)	3.28±0.18 (n=95)	3.29±0.18 (n=571)	0.63 (0.02)
WC (cm)	85.67±5.82 (n=6)	88.86±12.72 (n=95)	88.99±11.69 (n=571)	0.85 (0.06)
HC (cm)	100.33±8.82 (n=6)	101.28±10.13 (n=95)	102.06±9.90 (n=571)	0.71 (0.02)
WHR	0.85±0.04 (n=6)	0.88±0.07 (n=95)	0.89±0.35 (n=571)	0.97 (0.03)
SBP (mm Hg)	128.17±27.82 (n=6)	127.56±18.35 (n=95)	131.05±18.30 (n=571)	0.18 (0.13)
DBP (mm Hg)	75.33±11.02 (n=6)	78.70±13.62 (n=95)	82.71±11.68 (n=571)	0.006* (0.07)
LogTG	0.71±0.52 (n=2)	0.12±0.52 (n=59)	0.24±0.32 (n=403)	0.08 (0.15)
TC (mmol/l)	5.65±0.50 (n=2)	5.49±0.94 (n=59)	5.48±0.95 (n=403)	0.91 (0.02)
HDL-C (mmol/l)	1.08±0.06 (n=2)	1.36±0.26 (n=59)	1.29±0.27 (n=403)	0.05 (0.17)
LDL-C (mmol/l)	3.58±0.06 (n=2)	3.57±0.89 (n=59)	3.52±0.83 (n=403)	0.92 (0.01)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.3.3 Genetic effects of the ADRB2 rs1042717 on obesity in Malaysian Malays

ADRB2 rs1042717 is a synonymous SNP. Table 4.42 shows the genetic influence of the ADRB2 rs1042717 SNP on obesity parameters. There is no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards lower WC, DBP, TC and LDL-C compared to GG and AG carriers. The GG homozygotes showed trend towards lower logBMI, HC and SBP compared to AG and AA carriers. The GG homozygotes showed trend towards higher WHR and lower weight compared to AG and AA carriers. The AG heterozygotes showed trend towards lower logTG and HDL-C levels compared to GG and AA homozygotes. The AG heterozygotes showed trend towards higher weight compared to GG and AA homozygotes; the AA homozygotes showed trend towards lower height compared to AG and GG carriers.

Table 4.42 : Genetic effects of the ADRB2 rs1042717 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.59±0.09 (n=204)	1.59±0.09 (n=345)	1.58±0.10 (n=121)	0.81 (0.51)
Weight(kg)	67.48±12.82 (n=204)	68.87±14.69 (n=345)	68.33±13.50 (n=121)	0.36 (0.08)
LogBMI	3.27±0.18 (n=204)	3.29±0.18 (n=345)	3.29±0.18 (n=121)	0.58 (0.02)
WC (cm)	88.87±12.25 (n=204)	89.29±11.77 (n=345)	88.20±11.12 (n=121)	0.70 (0.06)
HC (cm)	101.32±9.47 (n=204)	102.27±10.25 (n=345)	102.00±10.69 (n=121)	0.52 (0.02)
WHR	0.88±0.08 (n=204)	0.87±0.07 (n=345)	0.87±0.08 (n=121)	0.36 (0.25)
SBP (mm Hg)	129.42±18.98 (n=204)	131.31±18.72 (n=345)	130.04±16.52 (n=121)	0.66 (0.12)
DBP (mm Hg)	81.49±12.78 (n=204)	82.68±11.96 (n=345)	81.23±10.92 (n=121)	0.43 (0.06)
LogTG	0.23±0.58 (n=141)	0.22±0.54 (n=241)	0.23±0.60 (n=81)	1.00 (0.12)
TC (mmol/l)	5.45±1.02 (n=141)	5.53±0.94 (n=241)	5.42±0.86 (n=81)	0.54 (0.03)
HDL-C (mmol/l)	1.32±0.29 (n=141)	1.28±0.26 (n=241)	1.32±0.27 (n=81)	0.11 (0.17)
LDL-C (mmol/l)	3.46±0.89 (n=141)	3.59±0.82 (n=241)	3.43±0.78 (n=81)	0.20 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.3.4 Genetic effects of the ADRB2 rs1042718 on obesity in Malaysian Malays

ADRB2 rs1042718 is a synonymous SNP. Table 4.43 shows the genetic influence of the ADRB2 rs1042718 SNP on obesity parameters. There is no significant difference among the subjects having CC, CA and AA in all the obesity and obesity-related parameters after adjustment for age and gender. The AA homozygotes showed trend towards lower height, WC, WHR, TC and LDL-C compared to CC and CA carriers. The CC homozygotes showed trend towards lower weight, logBMI, HC, SBP and DBP compared to CA and AA carriers. The CA heterozygotes showed trend towards lower logTG and HDL-C levels compared to CC and AA homozygotes.

Table 4.43 : Genetic effects of the ADRB2 rs1042718 on obesity parameters

Parameter	CC	CA	AA	p (R ²)
Height(m)	1.59±0.09 (n=208)	1.59±0.09 (n=339)	1.58±0.10 (n=123)	0.86 (0.51)
Weight(kg)	67.22±12.23 (n=208)	68.88±15.08 (n=339)	68.60±13.93 (n=123)	0.22 (0.08)
LogBMI	3.27±0.18 (n=208)	3.29±0.19 (n=339)	3.29±0.17 (n=123)	0.33 (0.03)
WC (cm)	88.87±11.93 (n=208)	89.25±11.79 (n=339)	88.35±11.66 (n=123)	0.90 (0.06)
HC (cm)	101.20±9.24 (n=208)	102.31±10.47 (n=339)	102.14±9.43 (n=123)	0.39 (0.02)
WHR	0.88±0.08 (n=208)	0.87±0.08 (n=339)	0.86±0.08 (n=123)	0.38 (0.25)
SBP (mm Hg)	128.30±18.49 (n=208)	131.97±18.93 (n=339)	130.19±16.54 (n=123)	0.08 (0.13)
DBP (mm Hg)	80.55±11.98 (n=208)	83.18±12.39 (n=339)	81.49±11.00 (n=123)	0.04 (0.06)
LogTG	0.23±0.59 (n=142)	0.22±0.54 (n=238)	0.25±0.59 (n=83)	0.87 (0.12)
TC (mmol/l)	5.46±1.02 (n=142)	5.51±0.95 (n=238)	5.44±0.82 (n=83)	0.78 (0.03)
HDL-C (mmol/l)	1.32±0.29 (n=142)	1.28±0.26 (n=238)	1.31±0.28 (n=83)	0.14 (0.18)
LDL-C (mmol/l)	3.48±0.89 (n=142)	3.58±0.83 (n=238)	3.44±0.74 (n=83)	0.31 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.3.5 Genetic effects of the ADRB2 rs1042719 on obesity in Malaysian Malays

ADRB2 rs1042719 is a synonymous SNP. Table 4.44 shows the genetic influence of the ADRB2 rs1042719 SNP on obesity parameters. There is no significant difference among the subjects having CC, CG and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The GG homozygotes showed trend towards lower weight, logBMI, WC, HC, SBP and DBP compared to CG and CC carriers. The GG homozygotes showed trend towards higher logTG and HDL-C compared to CG and CC carriers. The CG carriers showed trend towards higher height and LDL-C compared to GG and CC carriers. The CG carriers showed trend towards lower logTG and higher height compared to GG and CC carriers. The CC homozygotes showed trend towards lower TC compared to CG and CC carriers.

Table 4.44 : Genetic effects of the ADRB2 rs1042719 on obesity parameters

Parameter	CC	CG	GG	p (R ²)
Height(m)	1.58±0.10 (n=194)	1.59±0.09 (n=351)	1.58±0.08 (n=125)	0.79 (0.51)
Weight(kg)	69.35±14.62 (n=194)	68.40±14.22 (n=351)	66.47±12.46 (n=125)	0.12 (0.08)
LogBMI	3.30±0.18 (n=194)	3.28±0.18 (n=351)	3.26±0.17 (n=125)	0.21 (0.03)
WC (cm)	89.53±11.51 (n=194)	88.90±11.34 (n=351)	88.25±13.45 (n=125)	0.59 (0.06)
HC (cm)	103.00±10.23 (n=194)	101.60±9.83 (n=351)	101.19±9.58 (n=125)	0.21 (0.02)
WHR	0.87±0.08 (n=194)	0.87±0.07 (n=351)	0.87±0.09 (n=125)	0.92 (0.25)
SBP (mm Hg)	131.18±17.60 (n=194)	130.35±18.38 (n=351)	129.93±19.83 (n=125)	0.77 (0.12)
DBP (mm Hg)	82.58±12.10 (n=194)	82.02±11.56 (n=351)	81.34±13.38 (n=125)	0.55 (0.06)
LogTG	0.23±0.56 (n=132)	0.22±0.56 (n=244)	0.24±0.57 (n=87)	0.98 (0.12)
TC (mmol/l)	5.38±0.92 (n=132)	5.52±0.95 (n=244)	5.52±0.99 (n=87)	0.30 (0.03)
HDL-C (mmol/l)	1.27±0.26 (n=132)	1.30±0.26 (n=244)	1.32±0.32 (n=87)	0.21 (0.17)
LDL-C (mmol/l)	3.43±0.79 (n=132)	3.57±0.85 (n=244)	3.54±0.88(n=87)	0.32 (0.02)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.3.6 LD and haplotype analysis of ADRB2 gene

The data from five ADRB2 SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.5 shows the LD pattern of ADRB2 gene. D prime value (D') of 1.0 shows the complete linkage disequilibrium. The boxes in red are with strong LD. The boxes with values of $D' < 1.0$ are in shades of pink or red. The strength of LD pattern in ADRB2 gene region was high. High LD were observed at ADRB2 rs1042713 SNP with ADRB2 rs1042717 SNP ($D'=0.90$) and rs1042718 ($D'=0.94$); rs1042714 with rs1042717 ($D'=0.86$), rs1042718 ($D'=0.87$) and rs1042719 ($D'=0.81$); rs1042717 with rs1042718 ($D'=0.87$) and rs1042719 ($D'=0.88$) and rs1042718 with rs1042719 ($D'=0.93$). Low LD were observed at ADRB2 rs1042713 SNP with ADRB2 rs1042714 ($D'=0.67$) and rs1042719 ($D'=0.56$) SNPs.

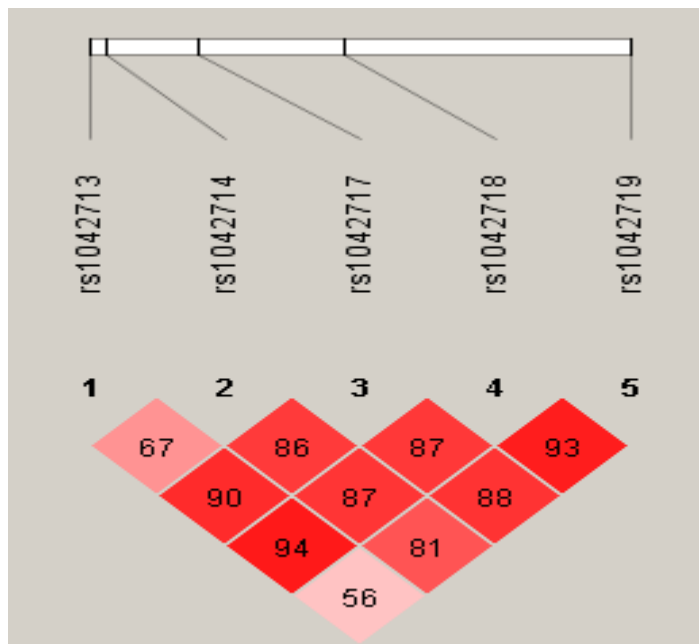


Figure 4.5 : LD pattern of ADRB2 gene in non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 5 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

LD analysis was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.6 shows the haplotype block and LD pattern of MC4R gene in the obese subjects. It was observed that the LD pattern of MC4R gene in the non-obese subjects is similar to that of the non-obese and obese subjects.

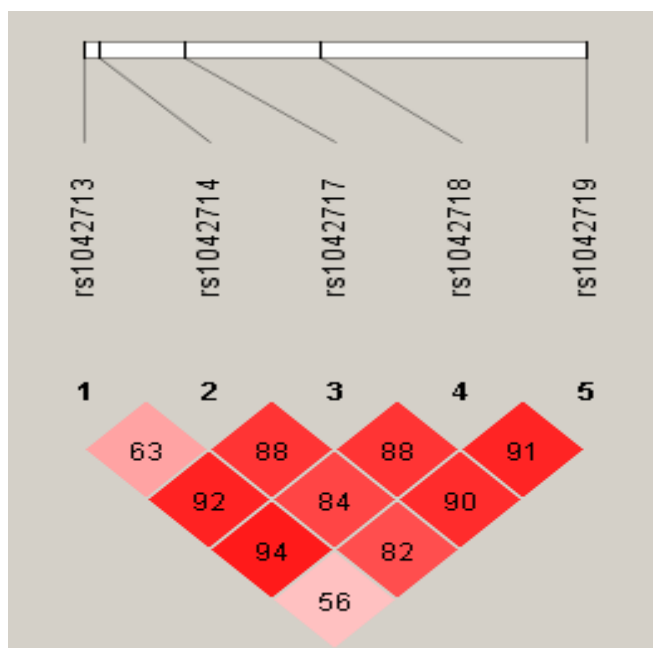


Figure 4.6 : LD pattern of ADRB2 gene in non-obese participants

*The figure shows the linkage disequilibrium pattern among 5 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

A haplotype block found in the ADRB2 gene region in this study. There are 8 haplotypes found in the chromosomal region of the ADRB2 gene. Four ADRB2 haplotypes had high frequencies (more than 5%) while four haplotypes had low frequencies (less than 5%). ADRB2 haplotype GCAAC had higher haplotype frequency (0.84) and ACACG haplotype had lower haplotype frequency (0.02). The ADRB2 haplotypes were tested for association with obesity. Table 4.45 shows the block 1 of the ADRB2 haplotypes. The GCAAC, ACGCG, ACGCC and GGGCG haplotypes in the block 1 showed frequencies of 39%, 31% and 11% and 6% respectively. The GCGCG,

GCGAC and GCACC haplotypes had lower frequencies (<5%). There were no significant differences in ADRB2 haplotypes frequencies between obese and non-obese group. After correcting for permutation testing with 5000 permutations, none of the haplotypes were associated with obesity.

Table 4.45 : Association analysis of ADRB2 haplotype

Block	Freq.	Obese Freq	Non-obese Freq	χ^2	p Value
Block 1					
GCAAC	0.39	0.40	0.39	0.20	1.00
ACGCG	0.31	0.29	0.32	1.09	0.94
ACGCC	0.11	0.12	0.10	0.73	0.99
GGGCG	0.06	0.06	0.06	0.00	1.00
GCGCG	0.04	0.04	0.04	0.17	1.00
GCGAC	0.02	0.03	0.02	0.38	1.00
GCACC	0.01	0.01	0.02	0.20	1.00
ACACG	0.01	0.02	0.01	3.55	0.37

*p-values were determined using chi-square after correcting for 5000 permutations.

4.3.4 Genetic profiling of Leptin gene (LEP)

A total of eight LEP SNPs were genotyped in this study. Table 4.46 summarizes the obese and non-obese participants of the LEP SNPs. Five-thousand permutation test was performed to analyze the individual SNPs. The marker chromosome position, minor allele frequencies (MAF) and allele frequencies in obese and non-obese subjects of the 7 SNPs studied in the LEP gene are summarized in Table 4.46. Following LEP SNPs rs1349419, rs12535708, rs12535747, rs7799039 (G-2548A), rs2167270, rs2278815 and rs12706832 did not deviate from the Hardy-Weinberg equilibrium. However, the LEP rs11770725 SNP (p HWE case: control= 0.002/<0.001) SNP deviated from the Hardy-Weinberg equilibrium. Therefore, LEP rs11770725 SNP was removed from further analysis. After 5000 permutation test, no significant difference was found in allelic frequency of each of the LEP SNPs between the obese and non-obese group. The LEP rs12706832 SNP had the highest MAF (0.28). Similar MAF were observed in LEP rs1349419 and rs2278815 (0.25); rs12535708, rs12535747 and rs2167270 (0.25) SNPs.

Table 4.46 : Allelic distribution of LEP SNPs among obese and non-obese groups

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	p	HWE (P ^a /P ^b)
rs1349419	127877213	0.25	A	0.26	0.25	0.15	1.00	0.21/0.54
rs12535708	127878098	0.16	C	0.86	0.84	0.83	0.94	0.09/0.15
rs12535747	127878335	0.16	C	0.86	0.84	0.83	0.94	0.09/0.15
rs7799039	127878783	0.27	G	0.29	0.26	1.14	0.90	0.16/0.43
rs2167270	127881349	0.16	G	0.86	0.84	0.92	0.93	0.09/0.18
rs2278815	127881851	0.25	G	0.27	0.25	0.49	1.00	0.08/0.79
rs12706832	127887139	0.28	A	0.31	0.27	1.79	0.64	0.07/0.93

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- p value for HWE in obese/ p value for HWE in non-obese

* p -values were determined using chi-square test with 5000 permutation test

4.3.4.1 Genetic effects of the LEP rs1349419 on obesity in Malaysian Malays

LEP rs1349419 SNP is located at position 883 at chromosome 7. Table 4.47 shows the genetic influence of the LEP rs1349419 SNP on obesity parameters. There is a significant difference between the GG compared to AG and AA groups, with log-leptin after adjustment with age and gender. However, after Bonferroni correction ($\alpha=0.007$), no significant difference was found between the GG compared to AG and AA groups with log-leptin. The AA homozygotes showed trend towards higher weight, logBMI, HC and logTG compared to AG and GG carriers. The AA homozygotes showed trend towards lower WC, WHR, SBP, DBP, TC, LDL-C and log-leptin compared to AG and GG carriers. The AG heterozygotes showed trend towards lower HDL-C compared to AA and GG homozygotes. The GG homozygotes showed trend towards higher height compared to AG and AA carriers. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.47 : Genetic effects of LEP rs1349419 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.59±0.09 (n=306)	1.58±0.09 (n=189)	1.58±0.10 (n=38)	0.24 (0.48)
Weight(kg)	68.53±13.89 (n=306)	67.27±14.00 (n=189)	69.26±13.66 (n=38)	0.86 (0.45)
LogBMI	3.29±0.18 (n=306)	3.28±0.19 (n=189)	3.31±0.18 (n=38)	0.67 (0.56)
WC (cm)	89.31±11.15 (n=306)	88.79±12.84 (n=189)	88.75±11.13 (n=38)	0.65 (0.45)
HC (cm)	102.05±10.00 (n=306)	101.60±9.99 (n=189)	103.36±9.88 (n=38)	0.54 (0.03)
WHR	0.88±0.07 (n=306)	0.87±0.09 (n=189)	0.86±0.07 (n=38)	0.99 (0.32)
SBP (mm Hg)	130.12±17.49 (n=306)	131.22±19.74 (n=189)	129.25±20.94 (n=38)	0.07 (0.31)
DBP (mm Hg)	81.74±12.17 (n=306)	82.49±12.06 (n=189)	80.79±14.16 (n=38)	0.01 (0.49)
LogTG	0.18±0.56 (n=205)	0.26±0.54 (n=127)	0.35±0.42 (n=24)	0.20 (0.33)
TC (mmol/l)	5.49±0.87 (n=205)	5.49±0.90 (n=127)	5.48±1.03 (n=24)	0.70 (0.19)
HDL-C (mmol/l)	1.31±0.26 (n=205)	1.29±0.29 (n=127)	1.30±0.25 (n=24)	0.90 (0.37)
LDL-C (mmol/l)	3.55±0.77 (n=205)	3.52±0.81 (n=127)	3.48±0.92 (n=24)	0.92 (0.15)
Log-leptin	2.48±0.72 (n=15)	1.56±1.08 (n=10)	1.47±0.00 (n=1)	0.04 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.2 Genetic effects of the LEP rs12535708 on obesity in Malaysian Malays

LEP rs12535708 SNP is located at position 1768 of chromosome 7. Table 4.48 shows the genetic influence of the LEP rs12535708 SNP on obesity parameters. There is a significant difference between the CC compared AC and AA groups, with log-leptin after adjustment with age and gender. However, after Bonferroni correction no significant difference was found between the CC compared AC and AA groups with log-leptin. The AA homozygotes showed trend towards higher height, weight, HC, logTG and log-leptin compared to AC and CC carriers. The AA homozygotes showed trend towards lower WHR, SBP, DBP, TC, HDL-C and LDL-C compared to AC and CC carriers. The AC heterozygotes showed trend towards higher logBMI and lower WC compared to CC and AA homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.48 : Genetic effects of LEP rs12535708 on obesity parameters

Parameter	CC	AC	AA	p (R ²)
Height(m)	1.59±0.09 (n=387)	1.57±0.10 (n=127)	1.60±0.08 (n=19)	0.38 (0.44)
Weight(kg)	68.00±13.63 (n=387)	68.27±14.62 (n=127)	70.19±14.86 (n=19)	0.89 (0.45)
LogBMI	3.28±0.18 (n=387)	3.30±0.19 (n=127)	3.29±0.18 (n=19)	0.93 (0.55)
WC (cm)	89.17±11.74 (n=387)	88.83±11.91 (n=127)	89.08±11.43 (n=19)	0.57 (0.47)
HC (cm)	101.84±9.80 (n=387)	102.23±10.52 (n=127)	103.45±10.33 (n=19)	0.51 (0.51)
WHR	0.88±0.08 (n=387)	0.87±0.08 (n=127)	0.86±0.06 (n=19)	0.70 (0.37)
SBP (mm Hg)	130.15±18.20 (n=387)	131.61±19.62 (n=127)	128.58±18.61 (n=19)	0.23 (0.23)
DBP (mm Hg)	81.89±12.37 (n=387)	82.43±12.06 (n=127)	79.58±11.81 (n=19)	0.07 (0.38)
LogTG	0.19±0.55 (n=255)	0.28±0.54 (n=88)	0.36±0.37 (n=13)	0.46 (0.52)
TC (mmol/l)	5.50±0.87 (n=255)	5.50±0.97 (n=88)	5.27±0.65 (n=13)	0.12 (0.21)
HDL-C (mmol/l)	1.31±0.27 (n=255)	1.29±0.28 (n=88)	1.26±0.17 (n=13)	0.64 (0.35)
LDL-C (mmol/l)	3.56±0.78 (n=255)	3.52±0.87 (n=88)	3.31±0.71 (n=13)	0.32 (0.12)
Log-leptin	1.47±0.00 (n=1)	1.64±1.29 (n=6)	2.26±0.84 (n=19)	0.05 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.3 Genetic effects of the LEP rs12535747 on obesity in Malaysian Malays

LEP rs12535747 SNP is located at position 2005 at chromosome 7. Table 4.49 shows the genetic influence of the LEP rs12535747 SNP on obesity parameters. There was a significant difference between the CC compared to AC and AA groups, with log-leptin after adjustment with age and gender. However, after Bonferroni correction, no significant difference was found between the CC compared to AC and AA carriers with log-leptin and logTG. The AA homozygotes showed trend towards higher height, weight, HC, logTG and log-leptin compared to AC and CC carriers. The AA homozygotes showed trend towards lower WHR, SBP, DBP, TC, HDL-C and LDL-C compared to AC and CC carriers. The AC heterozygotes showed trend towards higher logBMI and lower WC compared to CC and AA homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.49 : Genetic effects of LEP rs12535747 on obesity parameters

Parameter	CC	AC	AA	p (R ²)
Height(m)	1.59±0.09 (n=387)	1.57±0.10 (n=127)	1.60±0.08 (n=19)	0.38 (0.44)
Weight(kg)	68.00±13.63 (n=387)	68.26±14.62 (n=127)	70.19±14.86 (n=19)	0.89 (0.45)
LogBMI	3.28±0.18 (n=387)	3.30±0.19 (n=127)	3.29±0.18 (n=19)	0.93 (0.55)
WC (cm)	89.17±11.91 (n=387)	88.83±11.90 (n=127)	89.08±11.43 (n=19)	0.57 (0.47)
HC (cm)	101.84±9.80 (n=387)	102.23±10.52 (n=127)	103.45±10.33 (n=19)	0.51 (0.51)
WHR	0.88±0.08 (n=387)	0.87±0.08 (n=127)	0.86±0.06 (n=19)	0.70 (0.37)
SBP (mm Hg)	130.15±18.20 (n=387)	131.61±19.62 (n=127)	128.58±18.61 (n=19)	0.23 (0.23)
DBP (mm Hg)	81.89±12.37 (n=387)	82.43±12.06 (n=127)	79.58±11.81 (n=19)	0.07 (0.38)
LogTG	0.19±0.55 (n=255)	0.28±0.54 (n=88)	0.36±0.37 (n=13)	0.05 (0.42)
TC (mmol/l)	5.50±0.87 (n=255)	5.50±0.97 (n=88)	5.27±0.65 (n=13)	0.12 (0.21)
HDL-C (mmol/l)	1.31±0.27 (n=255)	1.29±0.28 (n=88)	1.26±0.17 (n=13)	0.64 (0.35)
LDL-C (mmol/l)	3.56±0.77 (n=255)	3.52±0.87 (n=88)	3.31±0.71 (n=13)	0.32 (0.12)
Log-leptin	1.47±0.00 (n=1)	1.64±1.29 (n=6)	2.26±0.84 (n=19)	0.05 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.4 Genetic effects of the LEP rs7799039 on obesity in Malaysian Malays

LEP rs7799039 SNP is located at position 2453 of chromosome 7. Table 4.50 shows the genetic influence of the LEP rs7799039 SNP on obesity parameters. There is no significant difference among the subjects having GG, GA and AA in all the obesity and obesity-related parameters after adjustment for age, gender and log-leptin. The GG homozygotes showed trend towards higher height, weight, logBMI, HC, logTG, TC and log-leptin compared to GA and AA carriers. The GG homozygotes showed trend towards lower DBP and HDL-C compared to GA and AA carriers. The GA heterozygotes showed trend towards higher LDL-C and lower WC and SBP compared to AA and GG homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.50 : Genetic effects of LEP rs7799039 on obesity parameters

Parameter	AA	GA	GG	p (R ²)
Height(m)	1.58±0.09 (n=294)	1.58±0.09 (n=195)	1.61±0.09 (n=44)	0.76 (0.54)
Weight(kg)	67.72±13.47 (n=294)	67.88±14.87 (n=195)	72.01±11.72 (n=44)	0.82 (0.45)
LogBMI	3.28±0.17 (n=294)	3.28±0.20 (n=195)	3.31±0.18 (n=44)	0.93 (0.54)
WC (cm)	89.81±10.79 (n=294)	89.41±13.41 (n=195)	89.49±9.90 (n=44)	0.78 (0.42)
HC (cm)	101.74±9.68 (n=294)	102.06±10.48 (n=195)	103.25±9.74 (n=44)	0.90 (0.47)
WHR	0.87±0.08 (n=294)	0.87±0.08 (n=195)	0.87±0.07 (n=44)	0.47 (0.33)
SBP (mm Hg)	130.69±17.71 (n=294)	130.09±18.90 (n=195)	130.34±22.29 (n=44)	0.14 (0.16)
DBP (mm Hg)	82.33±11.45 (n=294)	81.70±12.35 (n=195)	80.43±16.48 (n=44)	0.54 (0.19)
LogTG	0.22±0.55 (n=200)	0.16±0.54 (n=123)	0.41±0.50 (n=33)	0.41 (0.21)
TC (mmol/l)	5.46±0.89 (n=200)	5.52±0.86 (n=123)	5.56±1.00 (n=33)	0.69 (0.01)
HDL-C (mmol/l)	1.31±0.29 (n=200)	1.32±0.24 (n=123)	1.20±0.26 (n=33)	0.31 (0.32)
LDL-C (mmol/l)	3.50±0.81 (n=200)	3.59±0.74 (n=123)	3.58±0.91 (n=33)	0.52 (0.03)
Log-leptin	1.47±0.00 (n=1)	1.69±1.11 (n=11)	2.44±0.74 (n=14)	0.93 (0.54)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.5 Genetic effects of the LEP rs2167270 on obesity in Malaysian Malays

LEP rs2167270 SNP is located at position 5019 of chromosome 7. Table 4.51 shows the genetic influence of the LEP rs2167270 SNP on obesity parameters. There is a significant difference between GG compared to GA and AA groups, with log-leptin and logTG with age and gender. However, after Bonferroni correction, no significant differences were found between GG compared to GA and AA carriers, with log-leptin and logTG. The AA homozygotes showed trend towards higher height, weight, HC, logTG and log-leptin compared to GA and GG carriers. The AA homozygotes showed trend towards lower WHR, SBP, DBP, TC, HDL-C and LDL-C compared to GA and GG carriers. The GA heterozygotes showed trend towards higher logBMI and lower WC compared AA and GG homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.51 : Genetic effects of LEP rs2167270 on obesity parameters

Parameter	GG	GA	AA	p (R ²)
Height(m)	1.59±0.09 (n=386)	1.57±0.10 (n=128)	1.60±0.08 (n=19)	0.38 (0.44)
Weight(kg)	67.98±13.64 (n=386)	68.34±14.59 (n=128)	70.19±14.86 (n=19)	0.89 (0.45)
LogBMI	3.28±0.18 (n=386)	3.30±0.19 (n=128)	3.29±0.18 (n=19)	0.93 (0.55)
WC (cm)	89.14±11.74 (n=386)	88.93±11.91 (n=128)	89.08±11.43 (n=19)	0.57 (0.47)
HC (cm)	101.84±9.81 (n=386)	102.21±10.49 (n=128)	103.45±10.33 (n=19)	0.51 (0.51)
WHR	0.88±0.08 (n=386)	0.87±0.08 (n=128)	0.86±0.06 (n=19)	0.70 (0.37)
SBP (mm Hg)	130.12±18.21 (n=386)	131.70±20.24 (n=128)	128.58±18.61 (n=19)	0.23 (0.23)
DBP (mm Hg)	81.85±12.37 (n=386)	82.53±12.06 (n=128)	79.58±11.81 (n=19)	0.07 (0.38)
LogTG	0.19±0.55 (n=254)	0.27±0.55 (n=89)	0.36±0.37 (n=13)	0.05 (0.42)
TC (mmol/l)	5.49±0.87 (n=254)	5.51±0.97 (n=89)	5.27±0.65 (n=13)	0.12 (0.21)
HDL-C (mmol/l)	1.31±0.27 (n=254)	1.29±0.28 (n=89)	1.26±0.17 (n=13)	0.64 (0.35)
LDL-C (mmol/l)	3.55±0.77 (n=254)	3.53±0.87 (n=89)	3.31±0.71 (n=13)	0.32 (0.12)
Log-leptin	1.47±0.00 (n=1)	1.64±1.29 (n=6)	2.26±0.84 (n=19)	0.05 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.6 Genetic effects of the LEP rs2278815 on obesity in Malaysian Malays

LEP rs2278815 SNP is located at position 5521 of chromosome 7. LEP rs2278815 SNP, is an intronic SNP. Table 4.52 shows the genetic influence of the rs2278815 SNP on obesity parameters. There is a significant difference between the GG compared to AA and AG carriers, with log-leptin and DBP after adjustment with age and gender. However, after Bonferroni correction ($\alpha=0.007$), no significant difference was found between the AA compared to GA and GG carriers, with log-leptin and DBP. The GG homozygotes showed trend towards higher weight, logBMI, logTG and TC compared to AA and AG heterozygotes. The GG homozygotes showed trend towards lower height, WHR, LDL-C and log-leptin compared to AA and AG heterozygotes. The AG heterozygotes showed trend towards higher SBP and lower WC, HC and HDL-C compared to AA and GG homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.52 : Genetic effect of LEP rs2278815 on obesity parameters

Parameter	AA	AG	GG	p (R ²)
Height(m)	1.59±0.09 (n=303)	1.58±0.09 (n=191)	1.57±0.10 (n=39)	0.24 (0.44)
Weight(kg)	68.51±13.93 (n=303)	67.35±13.99 (n=191)	69.12±13.44 (n=39)	0.86 (0.45)
LogBMI	3.28±0.18 (n=303)	3.28±0.19 (n=191)	3.32±0.18 (n=39)	0.67 (0.56)
WC (cm)	89.30±11.18 (n=303)	88.77±12.80 (n=191)	88.96±11.07 (n=39)	0.65 (0.45)
HC (cm)	102.05±10.03 (n=303)	101.50±9.86 (n=191)	103.88±10.14 (n=39)	0.54 (0.50)
WHR	0.88±0.07 (n=303)	0.87±0.09 (n=191)	0.86±0.07 (n=39)	0.99 (0.32)
SBP (mm Hg)	129.98±17.39 (n=303)	131.18±20.19 (n=191)	130.50±19.28 (n=39)	0.07 (0.31)
DBP (mm Hg)	81.68±12.16 (n=303)	82.37±12.37 (n=191)	81.82±12.86 (n=39)	0.01 (0.49)
LogTG	0.18±0.55 (n=204)	0.25±0.54 (n=129)	0.36±0.43 (n=23)	0.20 (0.33)
TC (mmol/l)	5.49±0.87 (n=204)	5.48±0.90 (n=129)	5.50±1.05 (n=23)	0.70 (0.19)
HDL-C (mmol/l)	1.31±0.26 (n=204)	1.29±0.28 (n=129)	1.30±0.26 (n=23)	0.90 (0.37)
LDL-C (mmol/l)	3.55±0.77 (n=204)	3.52±0.81 (n=129)	3.49±0.93 (n=23)	0.92 (0.15)
Log-leptin	2.48±0.72 (n=15)	1.56±1.08 (n=10)	1.47±0.00 (n=1)	0.04 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.7 Genetic effects of the LEP rs12706832 on obesity in Malaysian Malays

LEP rs12706832 is an intronic SNP. Table 4.53 shows the genetic influence of the LEP rs12706832 SNP on obesity parameters. There is a significant difference between AA compared to GG and AG groups, with log-leptin and DBP after adjustment with age and gender. However, after Bonferroni correction ($\alpha=0.007$), no significant differences were found between AA compared to GG and AG groups, with log-leptin and DBP. The AA homozygotes showed trend towards higher height, weight, logBMI, HC, TC, logTG, LDL-C and log-leptin compared to AG and GG carriers. The AA homozygotes showed trend towards lower WHR, SBP and HDL-C compared to AG and GG carriers. The AG heterozygotes showed trend towards higher WC compared to AA and GG homozygotes. The association between obesity parameters and SNP was also adjusted for log-leptin levels.

Table 4.53 : Genetics effects of LEP rs12706832 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.58±0.09 (n=281)	1.59±0.09 (n=205)	1.60±0.10 (n=47)	0.27 (0.47)
Weight(kg)	67.84±13.45 (n=281)	67.86±14.96 (n=205)	71.20±11.21 (n=47)	0.93 (0.45)
LogBMI	3.29±0.17 (n=281)	3.27±0.20 (n=205)	3.31±0.17 (n=47)	0.81 (0.55)
WC (cm)	88.73±10.73 (n=281)	89.56±13.33 (n=205)	89.11±10.07 (n=47)	0.67 (0.46)
HC (cm)	101.90±9.70 (n=281)	101.81±10.68 (n=205)	103.34±8.22 (n=47)	0.57 (0.51)
WHR	0.87±0.08 (n=281)	0.88±0.08 (n=205)	0.86±0.07 (n=47)	0.99 (0.33)
SBP (mm Hg)	130.58±19.06 (n=281)	130.35±19.06 (n=205)	130.02±20.25 (n=47)	0.06 (0.31)
DBP (mm Hg)	82.16±11.51 (n=281)	82.06±12.46 (n=205)	80.02±15.45 (n=47)	0.05 (0.40)
LogTG	0.22±0.54 (n=193)	0.17±0.54 (n=129)	0.39±0.52 (n=34)	0.18 (0.32)
TC (mmol/l)	5.46±0.89 (n=193)	5.49±0.85 (n=129)	5.64±1.00 (n=34)	0.71 (0.19)
HDL-C (mmol/l)	1.31±0.29 (n=193)	1.31±0.23 (n=129)	1.22±0.28 (n=34)	0.88 (0.34)
LDL-C (mmol/l)	3.50±0.82 (n=193)	3.56±0.73 (n=129)	3.65±0.93 (n=34)	0.93 (0.16)
Log-leptin	1.47±0.00 (n=1)	1.69±1.11 (n=10)	2.44±0.74 (n=15)	0.04 (0.67)

* Adjusted for age, gender and log-leptin

*p-values were determined using General Linear Model

4.3.4.8 LD and haplotype analysis of LEP gene

The data from seven LEP SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.7 shows the haplotype block and LD pattern of the leptin gene. D prime value (D') of 1.0 shows a complete linkage disequilibrium. D' values of 1.0 are not shown (the box is empty with no value). The boxes should be a bright red colour when D' values are 1.0. The boxes in red are therefore with strong LD. The boxes with values of $D' < 1.0$ are in shades of pink or red. A haplotype block of 9kb was found at LEP gene region. The SNPs in this region are in strong LD. The haplotype block consists of six regions with complete LD ($D'=1.0$). Complete LD was observed at rs1349419 with rs12535708, rs2167270 and rs12535747; rs12535708 with rs12535747 and rs2167270 and rs12535747 with rs2167270.

High LD were observed at rs1349419 with rs7799039 ($D'=0.99$), rs12706832 ($D'=0.97$) and rs2278815 ($D'=0.99$); rs12535708 with rs7799039 ($D'=0.99$), rs2278815 ($D'=0.99$) and rs12706832 ($D'=0.95$); rs12535747 with rs7799039 ($D'=0.99$), rs2278815 ($D'=0.99$) and rs12706832 ($D'=0.95$); rs7799039 with rs2167270 ($D'=0.99$), rs2278815 ($D'=0.99$) and rs12706832 ($D'=0.97$); rs2167270 with rs2278815 ($D'=0.99$) and rs12706832 ($D'=0.95$); rs2278815 with rs12706832 ($D'=0.97$).

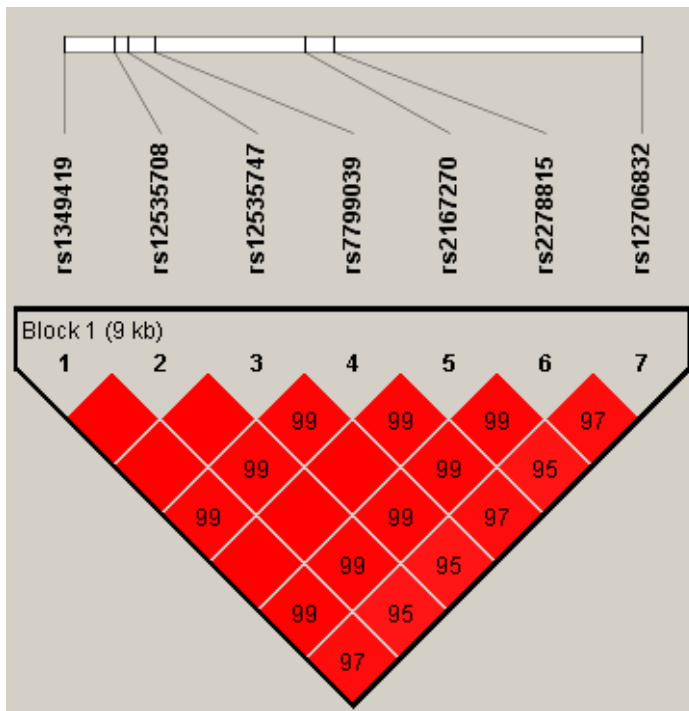


Figure 4.7 : Haplotype blocks of Leptin gene in non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 7 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

LD analysis of LEP gene was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.8 shows the haplotype block and LD pattern of LEP gene in the obese participants. It was observed that the LD pattern of LEP gene in the non-obese participants is similar to that of the non-obese and obese participants.

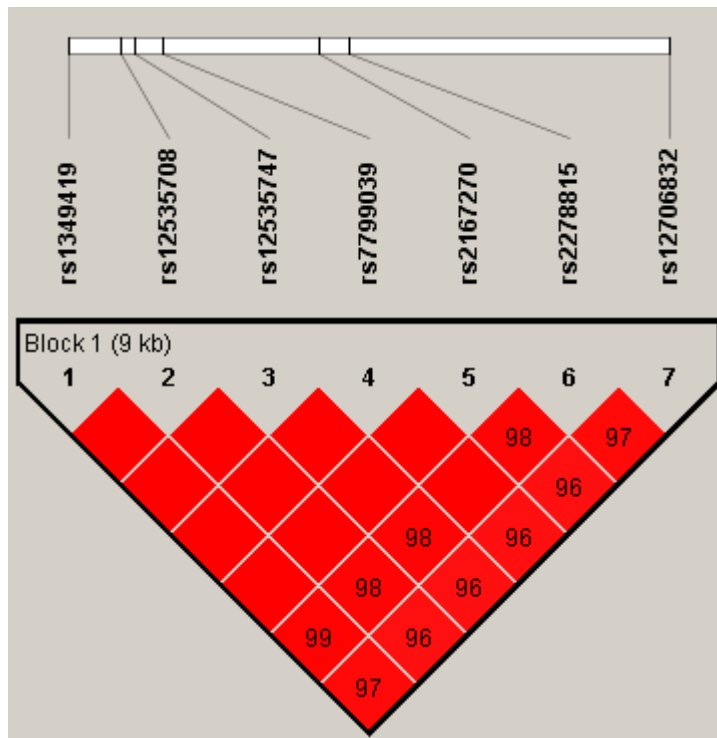


Figure 4.8 : Haplotype blocks of Leptin gene in non-obese participants

*The figure shows the linkage disequilibrium pattern among 7 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

There are five haplotypes found in the chromosomal region of the LEP gene. Three LEP haplotypes had high frequencies (more than 5%) while two LEP haplotypes had low frequencies (less than 5%). LEP haplotype GCCAGAG had highest frequency (0.72%) while GCCGGAA haplotypes had the lowest frequency (0.01).

The LEP haplotypes were tested for association with obesity. Table 4.54 shows the block 1 of the LEP haplotypes. The GCCAGAG, AAAGAGA, ACCGGGA, GCCAGAA and GCCGGAA haplotypes in the block 1 showed frequencies of 72%, 15%, 9%, 2% and 1% respectively. The GCCAGAA and GCCGGAA haplotypes had lower frequencies (<5%). There is a significant difference in haplotype frequencies of GCCGGAA between obese and non-obese group. After correcting for permutation testing with 5000 permutations, the GCCGGAA haplotypes was associated with obesity ($p=0.021$).

Table 4.54 : Association analysis of Leptin haplotype

Block	Freq	Obese Freq	Non-obese Freq	χ^2	p
Block 1					
GCCAGAG	0.72	0.69	0.73	1.24	0.84
AAAGAGA	0.15	0.13	0.16	1.12	0.90
ACCGGGA	0.09	0.11	0.08	2.18	0.60
GCCAGAA	0.02	0.02	0.02	0.09	1.00
GCCGGAA	0.01	0.03	0.01	8.83	0.02

**p*-values were determined using chi-square after correcting for 5000 permutations.

4.3.5 Genetic profiling of resistin (RETN) gene

A total of three RETN SNPs were genotyped in this study. Table 4.55 summarizes the allele frequencies in the obese and non-obese participants of the RETN SNPs. Five-thousand permutation test was performed to the individual SNPs. The marker chromosome position, minor allele frequencies (MAF) and allele frequencies in the obese and non-obese subjects of the 3 SNPs studied in the RETN are summarized in Table 4.55. Table 4.55 shows that the following RETN SNPs rs34861192, rs1862513 and rs3219175 SNPs did not deviate from the Hardy-Weinberg equilibrium. After 5000 permutation test, no significant difference was found in allelic frequency of each of the RETN SNPs between the obese and non-obese group. The RETN rs1862513 SNP had the highest MAF (0.46) and RETN rs3219175 SNP had the lowest MAF (0.14).

Table 4.55 : Allelic distribution of RETN SNPs among obese and non-obese groups

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	<i>p</i>	HWE (P ^a /P ^b)
rs34861192	7733575	0.15	G	0.87	0.84	1.33	0.50	0.43/0.96
rs1862513	7733793	0.46	C	0.47	0.46	0.13	0.95	0.50/0.98
rs3219175	7733855	0.14	G	0.87	0.85	0.57	0.76	0.43/0.79

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test with 5000 permutation test

4.3.5.1 Genetic effect of the RETN rs34861192 on obesity in Malaysian Malays

RETN rs34861192 SNP is located near 5' terminus of the RETN gene. Table 4.56 shows the genetic influence of the RETN rs34861192 SNP on obesity parameters. There is a significant difference between the GG compared to GA and AA carriers, with weight, logBMI, WC, HC and log-resistin after adjustment with age, gender, log-resistin and Bonferroni correction. The AA homozygotes had significantly higher WC and HC and lower weight and logBMI compared to GA and GG carriers. The AA homozygotes showed trend towards higher WHR, SBP and DBP compared to GA and GG carriers. The AA homozygotes showed trend towards lower height, TC, LDL-C, logHDL and logTG compared to GA and GG carriers.

Table 4.56 : Genetic effects of the RETN rs34861192 on obesity parameters

Parameter	GG	GA	AA	p (R ²)
Height(m)	1.59±0.09 (n=451)	1.59±0.09 (n=159)	1.52±0.11 (n=15)	0.16 (0.47)
Weight(kg)	69.02±14.23 (n=451)	67.78±12.61 (n=159)	61.47±16.20 (n=15)	0.01 (0.18)
LogBMI	3.29±0.18 (n=451)	3.28±0.17 (n=159)	3.24±0.22 (n=15)	0.03 (0.12)
WC (cm)	89.26±11.20 (n=451)	88.54±11.02 (n=159)	90.71±14.74 (n=15)	0.001 (0.23)
HC (cm)	102.31±9.80 (n=451)	101.26±8.84 (n=159)	102.64±16.03 (n=15)	<0.001 (0.29)
WHR	0.87±0.07 (n=451)	0.87±0.07 (n=159)	0.88±0.07 (n=15)	0.84 (0.40)
SBP (mm Hg)	130.83±18.70 (n=451)	130.20±16.87 (n=159)	135.00±12.78 (n=15)	0.63 (0.10)
DBP (mm Hg)	82.31±12.02 (n=451)	81.97±12.02 (n=159)	84.07±10.80 (n=15)	0.54 (0.10)
TC (mmol/L)	5.54±0.95 (n=316)	5.39±0.90 (n=119)	4.64±0.63 (n=5)	0.32 (0.13)
LDL-C (mmol/l)	3.58±0.85 (n=316)	3.41±0.76 (n=119)	2.92±0.71 (n=5)	0.26 (0.13)
LogHDL	0.24±0.20 (n=316)	0.24±0.21 (n=119)	0.20±0.15 (n=5)	0.95 (0.13)
LogTG	0.22±0.56 (n=316)	0.26±0.57 (n=119)	0.05±0.26 (n=5)	0.73 (0.16)
Log-resistin	-3.19±0.59 (n=69)	-2.67±0.60 (n=23)	-1.56±0.00 (n=1)	<0.001* (0.18)

* Adjusted for age, gender and log-resistin

*P-values were determined using General Linear Model

Due to smaller number of AA homozygotes compared to GG and GA carriers, effects of RETN rs34861192 SNP on obesity parameters was retested using dominant genetic model adjusting for age, gender and log-resistin. Table 4.57 showed that for the RETN rs34861192 SNP, there is a significant difference between the GG compared to A allele carriers, with log-resistin and weight after adjustment with age, gender, and Bonferroni correction. There is a significant difference between the GG homozygotes compared to A allele carriers with log-resistin. The GG homozygotes had significantly higher weight compared to A allele carriers. The GG homozygotes showed trend towards higher height, logBMI, WC, HC, SBP and DBP, TC and LDL-C compared A allele carriers. The A allele carriers showed trend towards higher logTG compared GG homozygotes.

**Table 4.57 : Genetic effects of the RETN rs34861192 on obesity parameters
(Dominant)**

Parameter	GG	GA + AA	p (R²)
Height(m)	1.59±0.09 (n=132)	1.58±0.09 (n=493)	0.06 (0.47)
Weight(kg)	69.02±14.23 (n=132)	67.26±13.01 (n=493)	0.01 (0.16)
LogBMI	3.29±0.18 (n=132)	3.28±0.17 (n=493)	0.05 (0.08)
WC (cm)	89.26±11.20 (n=132)	88.72 ±11.34 (n=493)	0.06 (0.13)
HC (cm)	102.31±9.80 (n=132)	101.37±9.58 (n=493)	0.03 (0.11)
WHR (cm)	0.87±0.07 (n=132)	0.87±0.07 (n=493)	0.60 (0.40)
SBP (mm Hg)	130.83±18.70 (n=132)	130.59±16.59 (n=493)	0.64 (0.10)
DBP (mm Hg)	82.31±12.02 (n=132)	82.14±11.91 (n=493)	0.40 (0.10)
TC (mmol/L)	5.54±0.95 (n=81)	5.36±0.90 (n=335)	0.89 (0.11)
LDL (mmol/L)	3.58±0.85 (n=80)	3.38±0.76 (n=335)	0.97 (0.10)
LogHDL	0.24±0.20 (n=81)	0.24±0.21 (n=235)	0.76 (0.13)
LogTG	0.22±0.56 (n=81)	0.25±0.56 (n=235)	0.42 (0.16)
Log-resistin	-3.19±0.59 (n=24)	-2.62±0.63 (n=69)	<0.001* (0.18)

* Adjusted for age, gender and log-resistin

*P-values were determined using General Linear Model

4.3.5.2 Genetic effects of the RETN rs1862513 on obesity in Malaysian Malays

RETN rs1862513 SNP is located near the 5' terminus of RETN gene. Table 4.58 shows the genetic influence of the RETN rs1862513 SNP on obesity parameters. There is a significant difference between the CC compared to GC and GG groups, with log-resistin. However, after Bonferroni correction ($\alpha=0.017$), no significant difference was found between the CC compared to GC and GG groups with log-resistin. The GG homozygotes showed trend towards higher HC, TC, logTG and LDL-C compared to GC and CC carriers. The GG homozygotes showed trend towards lower SBP and logHDL compared to GC and CC carriers. The GC heterozygotes showed trend towards lower height, WC and logBMI compared to GG and CC homozygotes. The GC heterozygotes showed trend towards higher weight and DBP compared to GG and CC homozygotes. The CC homozygotes showed trend towards higher WHR compared to GC and GG carriers. The association between obesity parameters and SNP was also adjusted for log-resistin levels.

Table 4.58 : Genetic effects of the RETN rs1862513 on obesity parameters

Parameter	CC	GC	GG	p (R ²)
Height(m)	1.58±0.10 (n=132)	1.53±0.06 (n=315)	1.58±0.09 (n=178)	0.99 (0.49)
Weight(kg)	68.05±14.83 (n=132)	68.82±13.86(n=315)	68.38±13.35 (n=178)	0.12 (0.17)
LogBMI	3.29±0.18 (n=132)	3.28±0.18 (n=315)	3.29±0.18 (n=178)	0.17 (0.10)
WC (cm)	89.75±11.97 (n=132)	88.89±11.14 (n=315)	89.03±10.87 (n=178)	0.25 (0.13)
HC (cm)	102.36±10.77 (n=132)	101.70±9.32 (n=315)	102.46±9.71 (n=178)	0.70 (0.07)
WHR	0.88±0.08 (n=132)	0.87±0.07 (n=315)	0.87±0.07 (n=178)	0.12 (0.44)
SBP (mm Hg)	132.16±15.97 (n=132)	131.41±19.11 (n=315)	128.55±17.71 (n=178)	0.96 (0.11)
DBP (mm Hg)	81.79±10.74 (n=132)	82.67±12.11 (n=315)	81.88±12.65 (n=178)	0.35 (0.19)
TC (mmol/L)	5.40±0.98 (n=81)	5.50±0.96 (n=235)	5.52±0.86 (n=124)	0.29 (0.14)
LDL-C (mmol/l)	3.42±0.87 (n=81)	3.54±0.86(n=235)	3.56±0.75 (n=124)	0.35 (0.13)
LogHDL	0.24±0.23 (n=81)	0.25±0.21 (n=235)	0.22±0.17 (n=124)	0.48 (0.18)
LogTG	0.21±0.57 (n=81)	0.21±0.57(n=235)	0.28±0.52 (n=124)	0.55 (0.15)
Log-resistin	-2.77±0.68 (n=24)	-3.11±0.63 (n=45)	-3.19±0.59 (n=24)	0.05 (0.08)

* Adjusted for age, gender and log-resistin

*p-values were determined using General Linear Model

4.3.5.3 Genetic effects of the RETN rs3219175 on obesity in Malaysian Malays

RETN rs3219175 SNP is located near 5' terminus of the RETN gene. Table 4.59 shows the genetic influence of the RETN rs3219175 SNP on obesity parameters. There were significant differences between the GG compared to AG and AA carriers with weight, WC, HC and log-resistin after adjustment with age, gender, log-resistin and Bonferroni correction. The GG homozygotes had significantly higher weight compared to GA and AA carriers. The AA homozygotes had significantly higher WC and HC compared to GA and GG carriers. The AA homozygotes showed trend towards higher WHR, SBP and DBP compared to AG and GG carriers. The AA homozygotes showed trend towards lower height, logBMI, TC, LDL-C, logHDL and logTG compared to AG and GG carriers.

Table 4.59 : Genetic effects of the RETN rs3219175 on obesity parameters

Parameter	GG	AG	AA	p (R ²)
Height(m)	1.59±0.09 (n=458)	1.59±0.09 (n=154)	1.52±0.11 (n=13)	0.08 (0.48)
Weight(kg)	68.94±14.14 (n=458)	67.82±13.09 (n=154)	62.18±14.43 (n=13)	0.01 (0.18)
LogBMI	3.29±0.18 (n=458)	3.28±0.18 (n=154)	3.27±0.20 (n=13)	0.04 (0.11)
WC (cm)	89.24±11.13 (n=458)	88.40±11.41 (n=154)	92.92±13.05 (n=13)	0.001 (0.23)
HC (cm)	102.29±9.78 (n=458)	101.14±9.00 (n=154)	104.42±15.78 (n=13)	<0.001 (0.29)
WHR	0.87±0.08 (n=458)	0.87±0.07 (n=154)	0.89±0.07 (n=13)	0.88 (0.40)
SBP (mm Hg)	130.78±18.70(n=458)	130.53±16.80(n=154)	133.17±12.68 (n=13)	0.67 (0.10)
DBP (mm Hg)	82.31±12.04 (n=458)	82.07±11.98 (n=154)	82.67±10.61 (n=13)	0.46 (0.11)
TC (mmol/L)	5.53±0.95 (n=322)	5.40±0.91 (n=114)	4.65±0.73 (n=4)	0.32 (0.13)
LDL-C (mmol/l)	3.57±0.85 (n=322)	3.41±0.78 (n=114)	2.95±0.81 (n=4)	0.26 (0.13)
LogHDL	0.24±0.20 (n=322)	0.24±0.22 (n=114)	0.21±0.17 (n=4)	0.99 (0.12)
LogTG	0.22±0.56 (n=322)	0.26±0.56 (n=114)	0.02±0.23 (n=4)	0.65 (0.16)
Log-resistin	-3.19±0.59 (n=70)	-2.66±0.62 (n=22)	-1.56±0.00 (n=1)	<0.001* (0.19)

* Adjusted for age, gender and log-resistin

*p-values were determined using General Linear Model

Due to smaller number of AA homozygotes compared to GG and AG carriers, effects of RETN rs3219175 SNP on obesity parameters was retested using dominant genetic model adjusting for age and gender. The association between obesity parameters and SNP was also adjusted for log-resistin levels. Table 4.60 shows for the rs3219175 SNP, there is a significant difference between the GG compared to A allele carriers with log-resistin and weight after adjustment with age and gender. The GG homozygotes had significantly higher weight compared to A allele carriers. The GG homozygotes showed trend towards higher height, logBMI, WC, HC, SBP, DBP, TC and LDL-C compared to the A allele carriers. The A allele carriers showed trend towards higher logHDL and logTG compared to GG homozygotes.

Table 4.60 : Genetic effects of the RETN rs3219175 on obesity parameters (Dominant)

Parameter	GG	AG + AA	p (R ²)
Height(m)	1.59±0.09 (n=458)	1.58±0.10 (n=154)	0.03 (0.48)
Weight(kg)	68.94±14.14 (n=458)	67.31±13.21 (n=154)	0.01 (0.16)
LogBMI	3.29±0.18 (n=458)	3.28±0.18 (n=154)	0.07 (0.08)
WC (cm)	89.24±11.13 (n=458)	88.70±11.58 (n=154)	0.05 (0.13)
HC (cm)	102.29±9.78 (n=458)	101.32±9.63 (n=154)	0.02 (0.12)
WHR (cm)	0.87±0.07 (n=458)	0.87±0.07 (n=154)	0.69 (0.40)
SBP (mm Hg)	130.78±18.70 (n=458)	130.55±16.41 (n=154)	0.77 (0.09)
DBP (mm Hg)	82.31±12.04 (n=458)	82.06±11.86 (n=154)	0.30 (0.10)
TC (mmol/L)	5.53±0.95 (n=322)	5.38±0.92 (n=114)	0.96 (0.11)
LDL (mmol/L)	3.57±0.85 (n=322)	3.40±0.79 (n=114)	0.92 (0.10)
LogHDL	0.24±0.20 (n=322)	0.25±0.21 (n=114)	0.91 (0.12)
LogTG	0.22±0.56 (n=322)	0.25±0.55 (n=114)	0.35 (0.16)
Log-resistin	-3.19±0.59 (n=24)	-2.62±0.65 (n=69)	<0.001* (0.18)

* Adjusted for age, gender and log-resistin

*p-values were determined using General Linear Model

4.3.5.4 LD and haplotype analysis of RETN gene

The data from three RETN SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.9 shows the haplotype block and LD pattern of resistin gene. D prime value (D') of 1.0 shows the complete linkage disequilibrium. D'

values of 1.0 are not shown (the box is empty). The boxes in bright red are with D' values of 1.0. The boxes in red are with strong LD. The boxes with values of $D' < 1.0$ are in shades of pink or red. A haplotype block was found at the RETN gene region. RETN rs3219175 SNP was in complete LD with RETN rs1862513 SNP ($D'=1.0$). RETN rs3219175 SNP was in strong LD with RETN rs34861192 SNP ($D'=0.99$). Strong LD was also observed at RETN rs34861192 with rs1862513 SNPs ($D'=0.90$).

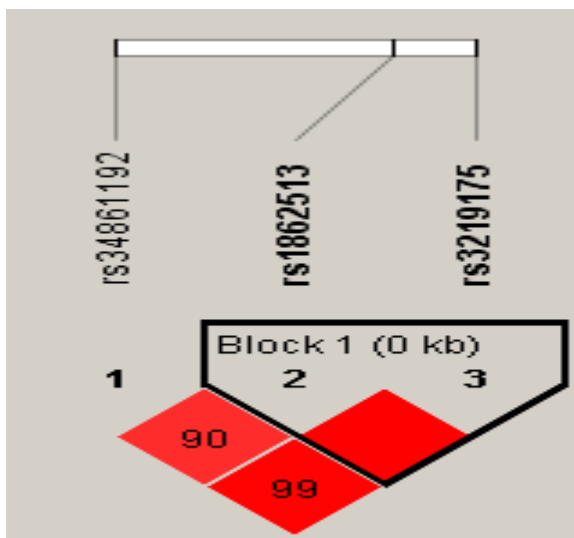


Figure 4.9 : Haplotype block of resistin gene in non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 3 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

LD analysis of RETN gene was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.10 shows the haplotype block and LD pattern of RETN gene in the non-obese subjects. It was observed that the LD pattern of RETN gene in the non-obese participants is similar to that of the non-obese and obese participants.

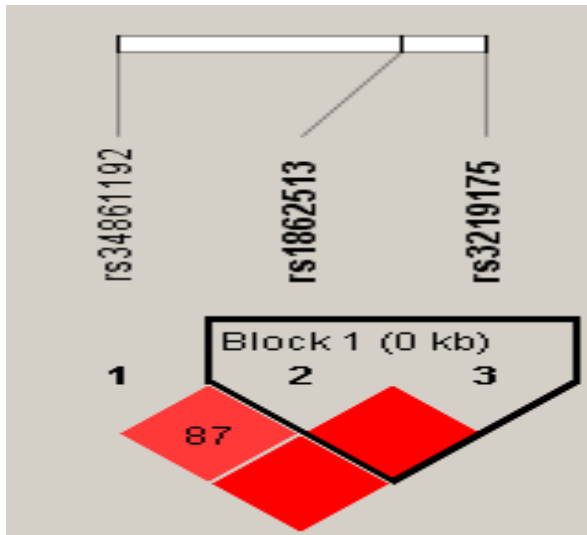


Figure 4.10 : Haplotype block of resistin gene in non-obese participants

*The figure shows the linkage disequilibrium pattern among 3 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

There are three haplotypes found in the chromosomal region of the RETN gene. All the three RETN haplotypes had high frequencies (> 5%). The GG haplotype had highest frequency (54%) and the CA haplotype had lowest frequency (14 %).

The RETN haplotypes were tested for association with obesity. Table 4.61 shows the block 1 of the RETN haplotypes. The GG, CG and CA haplotypes in the block 1 showed frequencies of 54%, 32% and 14% respectively. There is no significant difference in haplotype frequencies of RETN between obese and non-obese group. After correcting for permutation testing with 5000 permutations, the haplotypes were not associated with obesity.

Table 4.61 : Association analysis of resistin haplotype

Block	Frequencies	Obese, Frequencies	Non-obese, Frequencies	χ^2	p
Block 1					
GG	0.537	0.528	0.54	0.13	0.953
CG	0.319	0.341	0.312	0.909	0.633
CA	0.144	0.131	0.148	0.567	0.755

*p-values were determined using chi-square after correcting for 5000 permutations

4.3.6 Genetic profiling of insulin-induced gene (INSIG2)

One INSIG2 SNP was genotyped in this study. Table 4.62 shows the allele frequencies in the obese and non-obese participants of the INSIG2 rs7566605 SNP. Table 4.62 shows that the INSIG2 rs7566605 SNP did not deviate from the Hardy-Weinberg equilibrium. No significant difference was found between obese and non-obese groups for the allelic frequencies of INSIG2 rs7566605 SNP.

Table 4.62 : Allelic Distribution of INSIG2 rs7566605 SNP

SNP	Obese	Non-Obese	p	OR	95% CI	HWE (Pa/Pb)
rs7566605	C/G (0.56/0.44)	C/G (0.57/0.43)	0.75	0.98	[0.77~1.26]	0.69/0.43

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test

4.3.6.1 Genetic effects of the INSIG2 rs7566605 on obesity in Malaysian Malays

INSIG2 rs7566605 SNP is located 10kb upstream of INSIG2. Table 4.63 shows the genetic influence of the INSIG2 rs7566605 SNP on obesity parameters. There is no significant difference among the subjects having CC, GC and GG in all the obesity and obesity-related parameters after adjustment for age and gender. The CC homozygotes showed trend towards higher weight, WC, SBP and WHR compared to GC and GG carriers; the GG homozygotes showed trend towards higher logBMI, DBP, logTG, TC, LDL-C and HDL-C compared to CC and CG carriers.

Table 4.63 : Genetic effects of the INSIG2 rs7566605 on obesity parameters

Parameter	CC	GC	GG	p (R ²)
Height(m)	1.59±0.09 (n=213)	1.59±0.09 (n=336)	1.57±0.10 (n=123)	0.07 (0.52)
Weight(kg)	68.91±13.48 (n=213)	67.99±14.56 (n=336)	68.08±13.64 (n=123)	0.72 (0.08)
LogBMI	3.29±0.17 (n=213)	3.27±0.19 (n=336)	3.30±0.18 (n=123)	0.50 (0.03)
WC (cm)	89.61±11.49 (n=213)	88.66±11.57 (n=336)	88.54±12.92 (n=123)	0.79 (0.06)
HC (cm)	102.07±11.02 (n=213)	101.40±10.34 (n=336)	102.40±10.21 (n=123)	0.66 (0.03)
WHR	0.91±0.56 (n=213)	0.87±0.07 (n=336)	0.87±0.09 (n=123)	0.53 (0.04)
SBP (mm Hg)	130.93±18.75 (n=213)	130.19±17.90 (n=336)	130.75±19.31 (n=123)	0.96 (0.13)
DBP (mm Hg)	82.04±11.29 (n=213)	81.96±12.51 (n=336)	82.43±12.12 (n=123)	0.90 (0.06)
LogTG	0.20±0.54 (n=148)	0.23±0.58 (n=233)	0.25±0.56 (n=83)	0.59 (0.13)
TC (mmol/l)	5.39±0.91 (n=148)	5.49±1.01 (n=233)	5.62±0.81 (n=83)	0.19 (0.04)
HDL-C (mmol/l)	1.28±0.25 (n=148)	1.30±0.29 (n=233)	1.32±0.24 (n=83)	0.53 (0.16)
LDL-C (mmol/l)	3.48±0.79 (n=148)	3.51±0.92 (n=233)	3.63±0.67 (n=83)	0.49 (0.03)

* Adjusted for age and gender

*p-values were determined using General Linear Model

4.3.7 Genetic profiling of adiponectin gene (ADIPOQ)

Two ADIPOQ SNPs were genotyped in this study. Table 4.64 shows the allele frequencies in the obese and non-obese participants of the ADIPOQ SNPs. The ADIPOQ rs3774261 and rs17366568 SNPs did not deviate from the Hardy-Weinberg equilibrium. There was a significant difference between the obese and non-obese groups for the allelic frequencies of ADIPOQ rs17366568 SNP after 5000 permutation test. No significant difference was found between obese and non-obese groups for the allelic frequencies of ADIPOQ rs3774261 SNP.

Table 4.64 : Allelic Distribution of ADIPOQ SNPs

SNP ID	Chr	MAF	a	Obese Freq	Non-obese Freq	χ^2	<i>p</i>	HWE (P ^a /P ^b)
rs17366568	186570453	0.035	A	0.06	0.03	5.75	0.04	0.43/0.57
rs3774261	186571559	0.457	G	0.48	0.45	1.11	0.61	0.75/0.42

*Chr-Chromosome position of the SNP

*a –Associated allele

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**p*-values were determined using chi-square test with 5000 permutation test

4.3.7.1 Genetic effects of the ADIPOQ rs3774261 on obesity in Malaysian Malay

ADIPOQ rs3774261 SNP, is an intronic SNP. Table 4.65 shows the genetic influence of the ADIPOQ rs3774261 SNP on obesity parameters. There is no significant difference among the subjects having CC, GC and GG in all the obesity and obesity-related parameters after adjustment for age, gender and log-adiponectin. The CC homozygotes showed trend towards higher TC, HDL-C, LDL-C and log-adiponectin compared to GC and GG carriers; the GC heterozygotes showed trend towards higher height, SBP and DBP compared to CC and GG carriers; the GG homozygotes showed trend towards higher weight, WC, HC, logBMI and WHR compared to CC and GC carriers. The association between obesity parameters and SNP was also adjusted for log-adiponectin levels.

Table 4.65 : Genetic effects of the ADIPOQ rs3774261 on obesity parameters

Parameter	CC	GC	GG	p (R ²)
Height(m)	1.58±0.09 (n=179)	1.59±0.09 (n=324)	1.58±0.09 (n=136)	0.71 (0.47)
Weight(kg)	67.35±12.83 (n=179)	68.56±14.15 (n=324)	69.65±15.09 (n=136)	0.85 (0.11)
LogBMI	3.28±0.17 (n=179)	3.28±0.18 (n=324)	3.30±0.20 (n=136)	0.96 (0.08)
WC (cm)	88.55±10.93 (n=179)	88.81±11.68 (n=324)	90.95±12.81 (n=136)	0.59 (0.16)
HC (cm)	101.36±9.60 (n=179)	101.86±9.66 (n=324)	103.57±10.78 (n=136)	0.83 (0.12)
WHR	0.87±0.07 (n=179)	0.87±0.07 (n=324)	0.88±0.10 (n=136)	0.46 (0.39)
SBP (mm Hg)	130.03±17.80 (n=179)	130.97±18.88 (n=324)	129.46±16.70 (n=136)	0.79 (0.05)
DBP (mm Hg)	80.98±11.34 (n=179)	82.32±12.37 (n=324)	81.77±11.23 (n=136)	0.33 (0.11)
LogTG	0.15±0.52 (n=82)	0.27±0.56 (n=220)	0.26±0.61 (n=142)	0.31 (0.30)
TC (mmol/l)	5.55±1.00 (n=82)	5.44±0.96 (n=220)	5.52±0.89 (n=142)	0.88 (0.09)
HDL-C(mmol/l)	1.33±0.29 (n=82)	1.28±0.26 (n=220)	1.28±0.27 (n=142)	0.78 (0.21)
LDL-C (mmol/l)	3.61±0.89 (n=82)	3.48±0.83 (n=220)	3.53±0.81 (n=142)	0.84 (0.08)
Log-adiponectin	2.80±1.01 (n=29)	2.60±1.16 (n=47)	2.26±1.08 (n=25)	0.33 (0.10)

* Adjusted for age, gender and log-adiponectin

*p-values were determined using General Linear Model

4.3.7.2 Genetic effects of the ADIPOQ rs17366568 on obesity in Malaysian Malays

ADIPOQ rs17366568 SNP, is an intronic SNP. Table 4.66 summarizes the genetic influence of the ADIPOQ rs17366568 SNP on obesity parameters. There was no significant difference among the subjects having GG, AG and AA in all the obesity and obesity-related parameters after adjustment for age, gender and log-adiponectin. The AA homozygotes showed trend towards higher logweight, BMI, logHC, WC, SBP, DBP, TC, LDL-C, logHDL-C and logTG and lower height and WHR compared to AG and GG carriers; the AG heterozygotes showed trend towards lower log-adiponectin compared to AA and GG homozygotes.

Table 4.66 : Genetics effects of the ADIPOQ rs17366568 on obesity parameters

	GG	AG	AA	p (R²)
Height (m)	1.59±0.09 (n=535)	1.59±0.09 (n=38)	1.51±0.00 (n=1)	0.81 (0.48)
LogWeight	4.20±0.20 (n=535)	4.27±0.23 (n=38)	4.37±0.00 (n=1)	0.71 (0.11)
BMI (Kg/m²)	27.00±4.57 (n=535)	29.11±6.03 (n=38)	34.88±0.00 (n=1)	0.62 (0.07)
WC (cm)	89.18±11.52 (n=535)	91.55±13.24 (n=38)	97.00±0.00 (n=1)	0.24 (0.12)
LogHC	4.62±0.11 (n=535)	4.66±0.11 (n=38)	4.75±0.00 (n=1)	0.51 (0.11)
WHR	0.88±0.08 (n=535)	0.86±0.07 (n=38)	0.84±0.00 (n=1)	0.22 (0.36)
SBP (mm Hg)	130.52±18.09 (n=535)	129.64±15.38 (n=38)	156.00±0.00 (n=1)	0.69 (0.09)
DBP (mm Hg)	81.81±11.98 (n=535)	83.11±10.66 (n=38)	117.00±0.00 (n=1)	0.13 (0.74)
TC (mmol/l)	5.52±0.98 (n=369)	5.26±0.85 (n=31)	7.00±0.00 (n=1)	0.96 (0.08)
LDL(mmol/l)	3.54±0.86 (n=369)	3.33±0.82 (n=31)	4.75±0.00 (n=1)	0.68 (0.07)
LogHDL(mmol/l)	0.24±0.23 (n=369)	0.23±0.16 (n=31)	0.36±0.00 (n=1)	0.57 (0.20)
LogTG	0.25±0.55 (n=369)	0.20±0.61 (n=31)	0.59±0.00 (n=1)	0.74 (0.24)
Log-adiponectin	2.57±1.08 (n=369)	2.00±1.10 (n=31)	0	0.17 (0.06)

* Adjusted for age, gender and log-adiponectin

*p-values were determined using General Linear Model

Due to smaller number of AA homozygotes compared to GG and AG carriers, effects of ADIPOQ rs17366568 SNP on obesity parameters was retested using dominant genetic model adjusting for log-adiponectin, age and gender. Table 4.67 shows for the ADIPOQ rs17366568 SNP, there is no significant difference between GG compared to the A allele carriers, with obesity parameters. The A allele carriers showed trend towards higher logweight, BMI, WC, logHC and DBP compared to GG homozygotes; the GG homozygotes showed trend towards higher WHR, SBP, TC, LDL-C, logTG and log-adiponectin compared to the A allele carriers.

Table 4.67 : Genetics effects of the ADIPOQ rs17366568 on obesity parameters (Dominant)

	GG	AG + AA	p (R²)
Height (m)	1.59±0.09 (n=535)	1.59±0.09 (n=39)	0.81 (0.48)
LogWeight	4.20±0.20 (n=535)	4.28±0.23 (n=39)	0.71 (0.11)
BMI (Kg/m2)	26.94±4.54 (n=535)	29.26±6.02 (n=39)	0.62 (0.07)
WC (cm)	89.18±11.52 (n=535)	91.69±13.09 (n=39)	0.24 (0.12)
LogHC	4.62±0.11 (n=535)	4.66±0.11 (n=39)	0.51 (0.11)
WHR	0.88±0.08 (n=535)	0.86±0.07 (n=39)	0.22 (0.36)
SBP (mm Hg)	130.52±18.09 (n=535)	130.32±15.75 (n=39)	0.69 (0.09)
DBP (mm Hg)	81.81±11.98 (n=535)	83.97±11.84 (n=39)	0.13 (0.74)
TC (mmol/l)	5.52±0.98 (n=369)	5.31±0.89 (n=32)	0.96 (0.08)
LDL(mmol/l)	3.54±0.86 (n=369)	3.38±0.85 (n=31)	0.68 (0.07)
LogHDL(mmol/l)	0.24±0.23 (n=369)	0.24±0.16 (n=32)	0.57 (0.20)
LogTG	0.25±0.55 (n=369)	0.22±0.60 (n=32)	0.74 (0.24)
Log-adiponectin	2.57±1.08 (n=84)	2.00±1.10 (n=8)	0.17 (0.06)

* Adjusted for age, gender and log-adiponectin

*p-values were determined using General Linear Model

4.3.7.3 LD pattern and haplotypes of ADIPOQ gene

The data from two ADIPOQ SNPs was used to plot the LD pattern and to carry out a haplotype analysis. Figure 4.11 shows the haplotype block and LD pattern of ADIPOQ gene. D prime value (D') of 1.0 shows the complete linkage disequilibrium. The box with values of D' <1.0 is in shades of pink. A haplotype block was found at

ADIPOQ gene region. ADIPOQ rs17366568 SNP was in low LD with ADIPOQ rs3774261 SNP ($D'=0.65$).

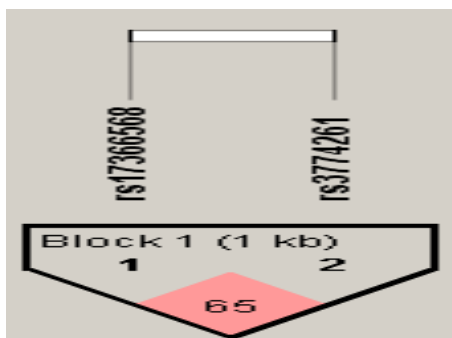


Figure 4.11 : Haplotype block of Adiponectin gene in non-obese and obese participants

*The figure shows the linkage disequilibrium pattern among 2 selected SNPs. Red denotes a significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

LD analysis of ADIPOQ gene was also performed separately in non-obese participants in order to check the difference between the LD pattern in the non-risk and risk participants. Figure 4.12 shows the haplotype block and LD pattern of ADIPOQ gene in the non-obese subjects. It was observed that the strength LD of ADIPOQ gene in the non-obese participants is lower than LD of the non-obese and obese participants.

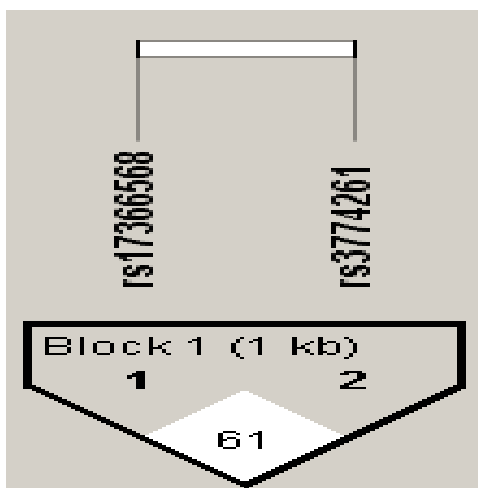


Figure 4.12 : Haplotype block of Adiponectin gene in non-obese participants

*The figure shows the linkage disequilibrium pattern among 2 selected SNPs. White denotes a non-significant linkage between an SNP pair. Numbers inside the square indicate $D' \times 100$

There are three haplotypes found in the chromosomal region of the ADIPOQ gene. Two of the haplotypes, GA and GG had high frequencies (> 5%). The GA haplotypes had highest frequency (54%) and the AG haplotype had lowest frequency (3%).

The ADIPOQ haplotypes were tested for association with obesity. Table 4.68 shows the block 1 of the ADIPOQ haplotypes. The GA, GG and AG haplotypes in the block 1 showed frequencies of 54%, 43% and 3% respectively. There is a moderate significant difference in AG haplotype frequencies of ADIPOQ between obese and non-obese group after correcting for permutation testing with 5000 permutations.

Table 4.68 : Association analysis of ADIPOQ haplotype

Block	Freq.	Obese Freq	Non-obese Freq	χ^2	p
Block 1					
GA	0.536	0.507	0.546	1.35	0.543
GG	0.429	0.436	0.427	0.08	0.978
AG	0.028	0.047	0.022	5.377	0.051

*p-values were determined using chi-square after correcting for 5000 permutations

4.3.8 Genetic profiling of SDC3 gene

SDC3 rs2491132 SNP, is a missense SNP. Table 4.69 summarizes the allele frequencies in the obese and non-obese subjects of the SDC3 rs2491132 SNP. The SDC3 rs2491132 SNP deviated from the Hardy-Weinberg equilibrium. No significant difference was found between obese and non-obese groups for the allelic frequencies of SDC3 rs2491132 SNP.

Table 4.69 : Allelic Distribution of SDC3 rs2491132 SNP

SNP	Obese	Non-obese	p	OR	95% CI	HWE (Pa/Pb)
rs2491132	C/T (0.88/0.12)	C/T (0.90/0.10)	0.34	0.83	[0.564~1.221]	<0.001/<0.001

P^a/P^b- *p* value for HWE in obese/ *p* value for HWE in non-obese

**P*-values were determined using chi-square test

4.4 Gene-gene interaction between FTO and MC4R

FTO rs17817288 and MC4R rs571312 SNPs were tested for gene-gene interaction. Table 4.70 shows that FTO rs17817288 and MC4R rs571312 SNPs were not significantly correlated to obesity parameters after Bonferroni correction ($\alpha=0.002$) and adjustment for age and gender.

Table 4.70 : Correlation between FTO rs17817288 and MC4R rs571312 SNPs

Parameter	p	R
Height(m)	0.25	-0.05
Weight(kg)	0.32	0.04
LogBMI	0.20	0.53
WC (cm)	0.17	0.06
HC (cm)	0.59	0.02
WHR	0.86	0.05
SBP (mm Hg)	0.02	0.00
DBP (mm Hg)	0.14	0.06
LogTG	0.50	0.03
TC (mmol/l)	0.22	-0.06
HDL-C (mmol/l)	0.24	-0.06
LDL-C (mmol/l)	0.18	0.07

*p-values were determined using Pearson's correlation test

FTO rs17817288 and MC4R rs2229616 SNPs were tested for gene-gene interaction. Table 4.71 shows that FTO rs17817288 and MC4R rs2229616 SNPs were not significantly correlated to obesity parameters after Bonferroni correction ($\alpha=0.002$) and adjustment for age and gender.

Table 4.71 : Correlation between FTO rs17817288 and MC4R rs2229616 SNPs

Parameter	<i>P</i>	<i>R</i>
Height(m)	0.27	-0.05
Weight(kg)	0.38	0.04
LogBMI	0.21	0.05
WC (cm)	0.29	0.04
HC (cm)	0.34	0.04
WHR	0.73	0.01
SBP (mm Hg)	0.88	0.01
DBP (mm Hg)	0.84	0.01
LogTG	0.35	-0.05
TC (mmol/l)	0.01	-0.12
HDL-C (mmol/l)	0.33	-0.05
LDL-C (mmol/l)	0.03	-0.11

**p*-values were determined using Pearson's correlation test

4.5 Analysis of obesity biomarkers

Three obesity biomarker levels were measured in this study. These biomarkers are leptin, adiponectin and resistin.

4.5.1 Correlation between biomarkers and obesity-related traits

Leptin, adiponectin and resistin were tested for correlation between obesity parameter such as waist circumference, hip circumference, waist-hip ratio, systolic blood pressure, diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, logBMI and logTG.

Table 4.72 shows the correlation between obesity biomarkers and obesity traits. Plasma log-adiponectin was positively correlated with HDL-C. Plasma log-adiponectin was negatively correlated with WC, HC, logBMI and logTG. Plasma log-leptin was positively correlated with WC, HC and logBMI. Plasma log-resistin was not significantly correlated with obesity-traits.

Table 4.72 : Correlation analysis of the biomarkers

Parameters	Log-adiponectin, p (R)	Log-resistin, p (R)	Log-leptin, p (R)
WC	0.01* (-0.27)	0.74 (-0.04)	0.02* (0.44)
HC	0.04* (-0.20)	0.67 (0.05)	<0.001* (0.64)
WHR	0.11 (-0.16)	0.33 (-0.10)	0.33 (0.11)
SBP	0.85 (0.02)	0.47 (-0.01)	0.46 (0.15)
DBP	0.73 (0.04)	0.88 (0.02)	0.54 (0.13)
TC	0.25 (-0.12)	0.25 (-0.12)	0.92 (0.02)
HDL-C	0.01* (0.26)	0.50 (0.07)	0.15 (0.29)
LDL-C	0.39 (-0.09)	0.15 (-0.15)	0.69 (-0.08)
LogBMI	0.02* (-0.23)	0.24 (-0.12)	<0.001* (0.69)
LogTG	<0.001* (-0.40)	0.92 (-0.01)	0.60 (0.11)

*p-values were determined using Pearson's correlation test

4.4.2 Gender effect of obesity biomarkers

The human leptin levels could not be detected in few of the plasma samples which were analyzed at the final stage of this study. This may be due to degradation of the bioactive human leptin during repeated freeze-thaw cycles. Variation in the levels of adiponectin, leptin and resistin in Malaysian Malay men and women were tested. Table 4.73 shows the gender effect of the leptin and BMI. There was no significant difference in BMI between men and women. There is a significant difference in leptin level between the genders. Leptin level is significantly higher in women compared to men.

Table 4.73 : Gender effect of Leptin and BMI

Parameter	Men	Women	p
Leptin ($\mu\text{g/ml}$)	4.66 \pm 3.81 (n=10)*	16.56 \pm 11.37 (n=16)*	<0.001
BMI (Kg/m^2)	23.30 \pm 4.43(n=10)	26.44 \pm 5.60 (n=16)	0.15

*p-values were determined using Mann-Whitney U test

*Undetectable for the remaining samples due to degraded proteins

Table 4.74 shows the gender effect of the adiponectin and resistin. There is no significant difference in adiponectin level between the genders. However, there is a trend towards lower adiponectin level in men compared to women. There is no significant difference in resistin level between the genders.

Table 4.74 : Gender effect of Adiponectin and resistin

Parameter	Men	Women	p
Adiponectin ($\mu\text{g/ml}$)	17.52 \pm 16.94 (n=44)	27.45 \pm 33.00 (n=57)	0.23
Resistin ($\mu\text{g/ml}$)	0.06 \pm 0.04 (n=40)	0.06 \pm 0.04 (n=54)	0.81

**p*-values were determined using Mann-Whitney U test

*Undetectable for the remaining samples due to degraded proteins