OBESITY STUDY IN MALAYSIAN MALAYS WITH FOCUS ON CANDIDATE GENES AND BIOMARKERS

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my parents, Mr. Apalasamy & Mrs. Subbamah,

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To Lord Shiva & Rudra
Abstract

Obesity is in rising prevalence globally and it has been associated with high mortality rate and other comorbidities. Obesity is a highly heritable disorder but genes responsible for hereditary variations remain to be largely elusive. Recent findings have shown that single nucleotide polymorphisms (SNPs) in the following genes predispose to the increased risk of obesity and obesity-related traits: leptin (LEP), melanocortin-4 receptor (MC4R), β2-adrenoeceptor (ADRB2), insulin-induced gene 2 (INSIG2), syndecan 3 (SDC3), fat mass and obesity associated (FTO), resistin (RETN) and adiponectin (ADIPOQ). Biomarkers such as adiponectin, leptin and resistin have been shown to be tightly linked to obesity related metabolic pathways. This study was aimed to investigate association between obesity and obesity-related parameters such as Body Mass Index (BMI), body weight, height, waist circumference, hip circumference, waist hip ratio, blood pressure, cholesterol and lipid parameters with SNPs and biomarker levels. A total of 672 Malaysian Malay subjects were studied. Genotyping was carried out using two methods, namely, Real-Time PCR Taqman® SNP genotyping assays and also Sequenom MassARRAY. Data were analyzed using SPSS 16.0 statistical software and Haploview version 4.2. After adjustment with age, gender, related biomarker levels and Bonferroni correction, the present study exhibited significant associations between FTO rs17817288 with LDL-Cholesterol; MC4R rs571312 with logBMI and systolic blood pressure; MC4R rs2229616 SNP with total cholesterol; ADRB2 rs1042714 SNP with diastolic blood pressure, RETN rs3219175 and rs34861192 SNPs with weight and log-resistin levels. Strong linkage disequilibrium (LD) pattern was observed in resistin, FTO, ADRB2 and LEP gene. There is low LD in ADIPOQ and MC4R gene regions in this population. The leptin haplotype designated as GCCCGAA in this study, was associated with obesity in
Malaysian Malays. This study suggests that the variants of the MC4R, ADRB2, LEP, RETN and FTO genes may have important roles for the development of obesity-related metabolic traits in the Malaysian Malay population. Levels of adiponectin and leptin in plasma were linked to obesity and metabolic abnormalities in Malaysian Malays but resistin appeared have less effect on obesity and metabolic abnormalities.
Abstrak

Obesiti kini adalah pada kadar yang semakin meningkat di seluruh dunia dan ianya dikaitkan dengan kadar kematian yang tinggi dan juga ko-morbiditi yang lain. Obesiti adalah satu gangguan kesihatan yang nilai pewarisannya amat tinggi tetapi faktor-faktor genetik utama yang benar-benar terlibat adalah sukar untuk dipastikan. Penemuan terkini telah menunjukkan bahawa polimorfisma-polimorfisma nukleotida tunggal (SNPs) pada gen-gen berikut mempengaruhi obesiti dan ciri-ciri yang berkaitan dengan obesiti: leptin (LEP), reseptor melanocortin-4 (MC4R), β2-adrenoseptor (ADRB2), perangsang insulin 2 (INSIG2), syndecan 3 (SDC3), gen kaitan jisim lemak dan obesiti (FTO), resistin (RETN) dan adiponectin (ADIPOQ). Biomarker seperti adiponectin, leptin dan resistin telah dikait rapat dengan laluan metabolik obesiti yang berkaitan. Tujuan kajian ini adalah untuk menyiasat perkaitan antara obesiti dan parameter-parameter yang berkaitan dengan obesiti seperti Index Jisim Badan, berat badan, ketinggian, lilitan pinggang, lilitan pinggul, nisbah pinggang pinggul, tekanan darah, kolesterol dan parameter lipid dengan SNP dengan aras biomarker. Sebanyak 672 subjek Melayu Malaysia telah dikaji. Ciri genotaip (“genotyping”) telah dijalankan dengan menggunakan dua cara iaitu Real-Time PCR Taqman® ujian SNP dan juga Sequenom MassARRAY. Data dianalisiskan dengan menggunakan SPSS 16.0 statistik perisian dan version Haploview 4.2. Selepas pelarasan dengan umur, jantina, aras biomarker dan pembetulan Bonferroni, kajian ini menunjukkan bahawa terdapat signifikans antara FTO rs17817288 dengan LDL-Kolesterol; MC4R rs571312 dengan logBMI dan dengan tekanan darah sistolik; MC4R rs2229616 dengan jumlah kolesterol; ADRB2 rs1042714 dengan tekanan darah sistolik; SNP-SNP RETN rs3219715 dan rs34861192 dengan berat badan dan tahap log-resistin. "Linkage disequilibrium" (LD) yang nyata diperhatikan bagi gen-gen resistin, FTO, ADRB2 dan
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Sincerely,

A. Yamunah Devi, 2012
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LIST OF ABBREVIATIONS AND SYMBOLS

µg-Microgram
µl-Microliter
ADIPOQ-Adiponectin
ADRB2-β2-adrenoceptor
AGRP-Agouti related peptide
ASW-African ancestry in Southwest USA
BDNF-Brain-derived neurotrophic factor
BMI- Body mass index
BSA-Bovine serum albumin
CADM2-Cell adhesion molecule 2
CETP-Cholesteryl ester transfer protein
CEU-Utah residents with Northern and Western European ancestry
CHB-Han Chinese in Beijing, China
CHD-Chinese in Metropolitan Denver, Colorado
CHD-Coronary heart disease
CHS-Singaporean Chinese
CNVs-Copy Number Variantions
CRP- C-reactive protein
CTNNBL1-Catenin beta like 1
CVD-Cardiovascular disease
D'-Coefficient of linkage disequilibrium
DBP-Diastolic blood pressure
dbSNP-The single nucleotide polymorphism database
df-Degree of freedom
DNA-Deoxyribonucleic acid
DRD2-Dopamine D2 receptor
EDTA-Ethylenediaminetetraacetic acid
ER-Endoplasmic reticulum
LIST OF ABBREVIATIONS AND SYMBOLS (Cont.).

ETV5-ets variant 5
FANCL-Fanconi anemia, complementation group L
FTO-Fat mass and obesity associated gene
GHRL-Ghrelin
GIANT-Genetic Investigation of Antropometric Traits Consortium
GIH-Gujarati Indians in Houston, Texas
GLM-General linear method
Gln-Glutamine
Glu-Glutamic acid
GNB3G-Protein beta 3 subunit gene
GNPDA2-Glucosamine-6-phosphate deaminase 2
GPRC5B-G protein-coupled receptor, family C, group 5, member B
GWAS-Genome-wide association studies
HapMap-Haplotype Map
HC-Hip Circumference
HDL-C-High density lipoprotein-cholesterol
HMG-CoA-3-hydroxy-3-methylglutaryl-coenzyme A
HRP-Horseradish Peroxidase
HWE-Hardy-Weinberg equilibrium
IDF-International Diabetes Federation
IL-1- Interleukin-1
IL-Interleukin-6
INSIG2-Insulin-induced gene 2
INS-Insulin
INS-Singaporean Indians
JPT-Japanese from Tokyo, Japan
KCTD15-Potassium channel tetramerisation domain containing 15
kg-kilogram
LDL-Low density lipoprotein
LIST OF ABBREVIATIONS AND SYMBOLS (Cont.).

LD-Linkage disequilibrium
LEPR-Leptin receptor
HSL (LIPE)-Hormone-sensitive lipase
LRP1B-Low density lipoprotein receptor-related protein 1B
LWK-Luhya in Webuye, Kenya
m/z-Mass-to-charge ratio
MAF-Minor allele frequency
MALDI-TOF-Matrix-assisted laser desorption ionization –time-of-flight
MAP2K5-Mitogen-activated protein kinase kinase 5
MAS-Singaporean Malays
MC4R- Melanocortin-4 receptor
MCP-1-Monocyte chemotactic protein-1
MEX-Mexican ancestry in Los Angeles, California
ml-milliter
m-meter
mRNA- Messenger ribonucleic acid
MTCH2-Mitochondrial carrier 2
MTMR9-Myotubularin related protein 9
NCR3C1-Glucocorticoid receptor
NEFA-Nonesterified fatty acid
NEGR1-Neuronal growth regulator 1
NHMS- Third National Health and Morbidity Survey
nl-nanoliter
nm-nanometer
NTRK2-Neurotrophic tyrosine kinase, receptor type 2
NUDT3-Nudix (nucleoside diphosphate linked moiety X)-type motif 3
OD-Optical Density
PAI-1-Plasminogen activator inhibitor
PBS-Phosphate buffered saline
LIST OF ABBREVIATIONS AND SYMBOLS (Cont.).

PC1-Proconvertase 1
pg-pigogram
POMC-Pro-opiomelanocortin
PPARγ-Peroxisome proliferator activated receptor γ
PRKD1-Protein kinase D1
QPCTL-Glutamyl-peptide cyclotransferase-like
r²-Correlation coefficient
RBP4-Retinol binding protein-4
RETN-Resistin
RPL27A-Ribosomal protein L27a
SBP-Systolic blood pressure
SCAP-SREBP cleavage-activating protein
SDC3-Syndecan 3
sdLDL-Small, dense low-density lipoprotein
SDS-Sequence Detection System
SGVP-Singaporean Genome Variation Project
SH2B1-Adaptor protein 1
SLC39A8-Solute carrier family 39 (zinc transporter), member 8
SNP-Single nucleotide polymorphism
SREBPs-Sterol regulatory element binding proteins
T2DM DM-Type 2 Diabetes mellitus
TC-Total cholesterol
TG-Triglyceride
TMB-Tetramethyl-benzidine
TMEM160-Transmembrane protein 160
TMEM18-Transmembrane protein 18
TNF-α-Tumor necrosis factor-alpha
TNNI3K-TNNI3 interacting kinase
TSI-Toscans in Italy
LIST OF ABBREVIATIONS AND SYMBOLS (Cont.).

UCP1-Uncoupling protein 1
UCP2-Uncoupling protein 2
UCP3-Uncoupling protein 3
UPR-Unfolded protein response
WC-Waist circumference
WHO- World Health Organization
WHR-Waist-Hip-Ratio
YRI-Yoruba in Ibadan, Nigeria
ZNF608-Zinc finger protein 608
α-MSH-α-melanocyte-stimulating hormone
β2-AR-β2-adrenergic receptor
β3-AR-β3-Adrenergic receptor
χ2-Chi square