APOL2 COPY NUMBER VARIATION AND *APOE* POLYMORPHISMS IN SCHIZOPHRENIA WITH OBESITY

BY

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INTERNATIONAL ISLAMIC UNIVERSITY MALAYSIA

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A thesis submitted in fulfillment of the requirement for the degree of Master's of Health Sciences (Medical Genetics)

Kulliyyah of Medicine
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ABSTRACT

Obesity is a major health issue among individuals with schizophrenia, contributing to increased morbidity, premature mortality and reduced quality of life. Emerging evidence suggests that the biological mechanisms linking obesity and schizophrenia may be influenced by shared genetic susceptibility. Since both conditions involve disruption in lipid metabolism and inflammation, apolipoprotein genes such as apolipoprotein L2 (*APOL2*) and apolipoprotein E (*APOE*) have been proposed to play a role in susceptibility to neuropsychiatric and metabolic disorders. However, the contribution of these genetic variations to schizophrenia and obesity in the Malaysian population remains unclear. This study aimed to assess the association of apolipoprotein genetic variants with schizophrenia and obesity. The research was carried out in two stages. Firstly, a pilot study was conducted to investigate the candidate genes in three schizophrenia patients with a strong family history. Their DNA samples were subjected to whole-genome sequencing, focusing on structural variations. The identified variants, including *CHRNA7*, *NRG1*, *NRXN1* and *APOL2,* were cross-referenced with Ensembl, ClinVar and UniProt. Although *CHRNA7* and *NRG1* were detected in two out of three patients, *APOL2* copy number variation (CNV) was prioritised for further analysis based on cross-reference findings due to its role in lipid metabolism, which provides a biological link between schizophrenia and metabolic dysregulation. In parallel, the *APOE* polymorphisms were included as an additional candidate variant of interest. In the second stage, a case-control association study on *APOL2* CNV and *APOE* polymorphisms was conducted involving a total of 185 schizophrenia patients and 222 controls stratified by obesity status (70 and 92 obese, respectively). The BMIs were classified based on the Malaysian Clinical Practice Guideline, Management of Obesity (2023), with obesity defined as BMI ≥27.5 kg/m^2. Both variants were analysed using the TaqMan RT-PCR assays. This study showed no association of *APOL2* CNV with schizophrenia or obesity. However, the *APOE* polymorphisms were found to be linked with the risk of schizophrenia and obesity in a gender-dependent manner. Specifically, the *APOE* ε4 allele increased the risk of schizophrenia in females (OR = 2.377, 95% CI: 1.225 – 4.613, p = 0.009), even after controlling for obesity (OR = 2.950, 95% CI: 0.997 – 8.727, p = 0.043) and also associated with an increased risk of obesity in schizophrenia (OR = 1.896, 95% CI: 1.090 – 3.298, p = 0.002), with this association retaining statistical significance only among males (OR = 2.660, 95% CI: 1.266 – 5.591, p = 0.008). In contrast, the *APOE* ε2 allele reduced the risk of obesity in schizophrenia (OR = 0.291, 95% CI: 0.109 – 0.775, p = 0.009), with statistical significance retained only among females (OR = 0.206, 95% CI: 0.043 – 0.990, p = 0.032). These findings suggest a complex genetic interplay between neuropsychiatric and metabolic disorders, especially regarding gender-specific effects. Therefore, these findings may contribute to future investigations exploring genetically informed therapeutic strategies to address schizophrenia and obesity. Further understanding of the role of these genes and their interactions may contribute to potential therapeutic targets, allowing personalised treatments in schizophrenia patients with obesity.

ملخص البحث

تُعدُ السُمنة من المشكلات الصحية الكبرى لدى مرضى انفصام الشخصية (والذي يُعرف أيضًا بالفُصام)، حيث تساهم في زيادة نسبة انتشار المرض، وحالات الوفاة المبكرة، وتدني جودة الحياة. تُشيرُ الأدلة الناشئة إلى أنَّ الآليات البيولوجية المرتبطة بالسمنة والفُصام من الممكن أن تتأثر في القابلية الجينية المشتركة للإصابة بالمرض. بما أن كلا المرضين يتضمنان اضطراب في عملية أيض الدهون، والالتهاب، فقد تم اقتراح أنَّ جينات البروتين الدهني مثل أبوليوبروتين إل ٢ (*APOL2*)، وأبوليوبروتين إي (*APOE*) قد تلعب دوراً في القابلية الجينية للإصابة بالاضطرابات العصبية النفسية، والأيضية. ومع ذلك، لا تزال مساهمة هذه التغييرات الجينية في الإصابة بكلٍ من السمنة والفصام في السكان الماليزيين غير واضحة. هدفت هذه الدراسة إلى تقييم الرابطة بين المتغيرات الجينية للأبوليوبروتين وبين مرضي الفُصام والسمنة. تم إجراء البحث في مرحلتين. في المرحلة الأولى، أُجريت دراسة ارشادية أولية لفحص الجينات المرشحة لدى ثلاثة من مرضى الفُصام، والذين لديهم تاريخاً طبياً عائلياً للإصابة بالمرض، حيث خضعت عينات الحمض النووي الخاصة بهم لتسلسل الجينوم الكامل، مع التركيز على التغييرات الهيكلية. تم مقارنة المتغيرات الجينية المحددة بما في ذلك *APOL2*, *NRXN1*, *NRG1*, *CHRNA7* مع قواعد البيانات Ensembl, ClinVar, UniProt. على الرغم من اكتشاف جينات *CHRNA7* و*NRG1* في اثنين من أصل ثلاثة مرضى، إلا أنَّه أُعطيت الأولوية لاختلاف عدد نسخ (CNV) *APOL2* وذلك لإجراء المزيد من التحاليل اعتماداً على نتائج المقارنة، وذلك بسبب دوره في عملية أيض الدهون، الذي يوفر رابطاً بيولوجياً بين مرض الفُصام واختلال عملية التنظيم الأيضي. بالتوازي مع ذلك، أُدرجت تعددات أشكال *APOE* كمتغير مرشح ذا أهمية. في المرحلة الثانية، تم إجراء دراسة ارتباط الحالة والضابطة على تغير عدد نسخ CNV *APOL2* وتعدد أشكال *APOE*، والتي شملت ١٨٥ مريضاً بالفُصام و٢٢٢ من الضوابط، والذين تم تصنيفهم حسب حالة السمنة إلى ٧٠ و٩٢ مصاباً بالسمنة على التوالي. تم تصنيف مؤشرات كتلة الجسم وفقاً إلى الدليل الإرشادي الماليزي للممارسة السريرية لإدارة السمنة، حيث عُرفت السمنة على أنها مؤشر كتلة الجسم ≤ ٢٧,٥ كغم| م٢. تم تحليل كلا المتغيرين باستخدام اختبارات TaqMan RT-PCR. أظهرت هذه الدراسة عدم وجود ارتباط بين متغير عدد نسخ *APOL2* وبين الفُصام أو السمنة. ومع ذلك وُجِدَ ارتباط بين تعدد أشكال *APOE* وبين خطر الإصابة بالفُصام أو السمنة بطريقة تختلف باختلاف نوع الجنس. وعلى وجه التحديد، زاد أليل *APOE* ε4 من خطرالإصابة بالفُصام عند الإناث $OR = 2.377, 95\% CI: 1.225 - 4.613, p = 0.009$)، حتى بعد ضبط متغير السمنة ($OR = 2.950, 95\% CI: 0.997 - 8.727$,

(OR = 1.896, 95% CI: 1.090 – 3.298, p = 0.002)، مع احتفاظ هذا الارتباط بدلالة إحصائية فقط بين الذكور(OR = 2.660, 95%CI: 1.266 – 5.591, p = 0.008) . وعلى النقيض، ارتبط أليل $APOE$ ε2 بتقليل خطر الإصابة بالسمنة (OR = 0.291, 95% CI: 0.109 – 0.775, p = 0.009)، مع احتفاظ هذا الارتباط بدلالة إحصائية فقط بين الإناث (OR = 0.206, 95% CI: 0.043 – 0.990, p = 0.032). تُشير هذه النتائج إلى وجود تفاعل جيني معقد بين الاضطرابات العصبية النفسية والاضطرابات الأيضية، خاصةً فيما يتعلق بالتأثيرات المرتبطة بنوع الجنس. ولذلك، من الممكن أن تساهم هذه النتائج في الدراسات المستقبلية؛ لاكتشاف استراتيجيات علاجية تستند إلى المعرفة الجينية لمعالجة الفُصام والسمنة. وبالتالي يساهم المزيد من الفهم لدور هذه الجينات، وتفاعلاتها في تحديد أهداف علاجية محتملة، مما يتيح توفر علاجات مخصصة لمرضى الفصام الذين يعانون من السمنة.

APPROVAL PAGE

I certify that I have supervised and read this study and that in my opinion, it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master of Health Sciences in Medical Genetics.

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Nour El Huda Abd Rahim
Supervisor

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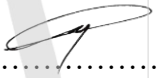
Norlelawati A. Talib
Co-Supervisor



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Mohd Asyraf Abdull Jalil
Co-Supervisor

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a thesis for the degree of Master's of Health Sciences (Medical Genetics).

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Nurul Ashikin Muhammad Musa
Examiner

Hisham Atan Edinur

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Edinur Hisham Atan
External Examiner

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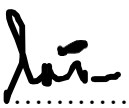

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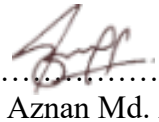
This thesis was submitted to the Kulliyyah of Medicine and is accepted as a fulfillment of the requirement for the degree of Master of Health Sciences (Medical Genetics)



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Dean, Kulliyyah of Medicine

DECLARATION

I hereby declare that this thesis is the result of my own investigations, except where otherwise stated. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at IIUM or other institutions.

Wan Noorainna Fatimi Wan Mohd Zani

Signature ……  …… Date …9th April 2026…

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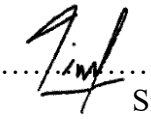

Signature

9th April 2026

Date

I dedicated this thesis to the people whose struggles with schizophrenia and obesity inspired every page of this work

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LIST OF ABBREVIATIONS

BMI	Body mass index
LDL	Low-density lipoprotein
SGA	Second-generation antipsychotic
APOA	Apolipoprotein A
APOB	Apolipoprotein B
APOC	Apolipoprotein C
APOD	Apolipoprotein D
APOE	Apolipoprotein E
APOF	Apolipoprotein F
APOH	Apolipoprotein H
APOL	Apolipoprotein L
APOM	Apolipoprotein M
APOO	Apolipoprotein O
APOE	Apolipoprotein E (gene)
APOL2	Apolipoprotein L2 (gene)
CNS	Central nervous system
MRI	Magnetic resonance imaging
DISC	Disrupted-In-Schizophrenia 1 (gene)
NRXN3	Neurexin 3 (gene)
GABA	Gamma-aminobutyric acid
ROS	Reactive oxygen species
NMDA	N-methyl-D-aspartate
IL-1β	Interleukin-1 beta
Indel	Insertion and deletion
CNV	Copy number variation
SNPs	Single-nucleotide polymorphisms
NGS	Next-generation sequencing
BWA	Burrows-Wheeler Aligner
WGS	Whole genome sequencing
WES	Whole exome sequencing
RNA-seq	RNA sequencing
ChIP-seq	Chromatic immunoprecipitation sequencing
ATAC-seq	Accessible chromatic sequencing
bp	Base pairs
Mb	Megabase pairs
COMT	Catechol-O-methyltransferase (gene)
ZDHHC8	Zinc finger DHHC-type containing 8 (gene)
DGCR8	DiGeorge syndrome critical region gene 8 (gene)
PRODH	Proline dehydrogenase 1 (gene)
Glx	Glutamate and Glutamine
GWAS	Genome-wide association study
ZNF804A	Zinc finger protein 804A (gene)
CCACNA1C	Calcium voltage-gated channel subunit alpha1 C (gene)
GRM1	Glutamate metabotropic receptor 1 (gene)
GABBR2	Gamma-aminobutyric acid type B receptor subunit 2 (gene)

GRIN2A	Glutamate ionotropic receptor NMDA type subunit 2A (gene)
FGA	First-generation antipsychotic
WHO	World Health Organisation
CPG	Clinical Practice Guidelines
FTO	Fat mass and obesity-associated (gene)
RalA	Ras-related protein Ral-A (gene)
DLK1	Delta-like non-canonical Notch ligand 1 (gene)
IL-6	Interleukin 6
CRP	C-reactive protein
SNV	Single-nucleotide variants
MCR4	Melanocortin-4-receptor (gene)
CM	Chylomicrons
VLDL	Very-low-density lipoprotein
IDL	Intermediate-density lipoprotein
HDL	High-density lipoprotein
Lp(a)	Lipoprotein (a)
LCAT	Lecithin-cholesterol acyltransferase
hs-CRP	High sensitive C-reactive protein
MPO	Myeloperoxidase
LDL-C	LDL-cholesterol
MAD	Membrane-addressing domain
PFD	Pore-forming domain
SID	SRA-interacting protein-like domain
IRG	Interferon-regulated gene
ER	Endoplasmic reticulum
VCFS	Velocardiofacial syndrome
OMIM	Online Mendelian Inheritance in Man
HTAA	Hospital Tengku Ampuan Afzan
DSM-5	Diagnostic and statistical manual for mental disorders-5
EDTA	Ethylenediaminetetraacetic
BGI	Beijing Genomics Institute
LM-PCR	Ligation-mediated polymerase chain reaction
RCA	Rolling circle amplification
DNB	DNA Nanoball
RT-PCR	Real-time polymerase chain reaction
RNAse P	Ribonuclease P (gene)
NTC	No template controls
FAM	Fluorescein amidites
Ct	Cycle threshold
RQ	Relative quantity
ACTB	β-actin
TE	Tris-EDTA
HEX	Hexachlorofluorescein
HWE	Hardy-Weinberg equilibrium
QC	Quality control
CHRNA7	Cholinergic receptor nicotinic alpha 7 subunit (gene)
NRG1	Neuregulin (gene)
NRXN1	Neurexin (gene)
Mb	Megabase
kb	kilobase

TF	Transcription factor
CCDS	Consensus coding sequences
ErbB	Erythroblastic Leukaemia Viral Oncogene Homolog
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
χ^2	Chi-squared
OR	Odds ratio
B	Regression coefficient
SE	Standard error
df	Degree of freedom