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ASSOCIATION BETWEEN FATTY LIVER-LINKED LYPLAL1 RS12137855 AND DEPRESSION IN TYPE 2 DIABETES: A 5-YEAR FOLLOW-UP ANALYSIS

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Angela Moh, [1]Serena Low,[1] Jianjun Liu,[1] Clara Tan,[1] Keven Ang, [1] Sylvia Liu,[1] Bhuvaneswari Pandian,[1] Tze Pin Ng, [2] Wern Ee Tang,[3] Ziliang Lim,[3] Tavintharan Subramaniam,[1]Chee Fang Sum,[1] Su Chi Lim[1]

[1]*Khoo Teck Puat Hospital, Singapore*
[2]*National University of Singapore, Singapore*
[3]*National Healthcare Group Polyclinics, Singapore*

INTRODUCTION
Limited data, predominantly cross-sectional, suggest an association between non-alcoholic fatty liver disease (NAFLD) and depression. Whether NAFLD-associated genetic variants are associated with depressive symptoms is not clearly defined, particularly in type 2 diabetes (T2D). Hence, this 5-year observational longitudinal study explored the relationship between four known NAFLD-linked single nucleotide polymorphisms (SNPs) and depression among multi-ethnic Asians with T2D.

METHODOLOGY
Participants diagnosed with T2D were recruited by the Singapore Study of Macroangiopathy and Microvascular Reactivity in Type 2 Diabetes (SMART2D) study from August 2011 to March 2014, and genotyped. The subjects were recalled from September 2014 to October 2017, during which baseline geriatric depression scale (GDS)-15 was administered and analyzed (n = 1,339; mean age: 62 ± 8 years, males: 52%). A follow-up GDS-15 assessment was conducted from Jul 2019 to May 2022. NAFLD was reflected by the hepatic steatosis index (HSI), which is a surrogate marker for fatty liver. Plasma specimens collected from September 2014 to October 2017 were subjected to nuclear magnetic resonance-based metabolomic profiling. PNPLA3 rs738409, NCAN rs2228603, LYPLAL1 rs12137855, GCKR rs780094, and their derived weighted-polygenic risk score (PRS) were evaluated.

RESULTS
Among the SNPs/PRS tested, only LYPLAL1 rs12137855 displayed increasing HSI readings from the CC to TT genotype (P36) than individuals harboring CT and CC genotypes (90.5%, 69.0% and 62.1%, respectively; $p = 0.004$). LYPLAL1 rs12137855 TT genotype was associated with baseline GDS-15 total score in the unadjusted (B = 1.28, 95% CI: 0.47–2.10; $P = 0.002$) and covariate-adjusted linear regression model (B=1.31, 95% CI: 0.48–2.14, $p = 0.002$), especially in the overweight/obesity category (body mass index ≥25 kg/m^2). Specifically, the SNP was associated with the depression dimensions of dysphoric mood, withdrawal-apathy-vigour, and hopelessness, but not with anxiety and memory complaints. Moreover, rs12137855 TT-alleles were associated with depression (GDS-15 ≥5; odds ratio=3.36, 95% CI: 1.03–10.96, $p = 0.044$) and absolute change in GDS-15 score after a mean 5-year follow-up period (B=1.57, 95% CI: 0.34–2.81, $p = 0.013$). The plasma metabolites that were associated with both GDS-15 and rs12137855 were valine, albumin, and proinflammatory glycoprotein acetyls. Using multiple mediation, we demonstrated that rs12137855 TT genotype was associated with the GDS-15 score through reduced albumin levels which accounted for 10.5% of the total effect.

CONCLUSION
LYPLAL1 rs12137855 TT genotype is associated with GDS-15-derived depression outcomes cross-sectionally and longitudinally in T2D. Given that LYPLAL1 rs12137855 is an intronic variant, it is unknown whether the SNP confers direct pathogenic consequences or indirectly through its linkage disequilibrium with a functional variant. Furthermore, the mood-depressive effect of this SNP appears to be mediated through reduced circulating albumin. Whether LYPLAL1 polymorphism plays a role in suppressing albumin synthesis and function that in turn affects mood warrants further investigation.

KEYWORDS
type 2 diabetes, fatty liver, depression