

Interleukin-13 rs20541 variant and obesity: From adipocyte mechanisms to population-level associations in Malaysia

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ABSTRACT

Obesity is a chronic inflammatory condition influenced by genetic and environmental factors. Interleukin-13 (IL-13), a cytokine involved in immune and metabolic regulation has a functional polymorphism, rs20541 (R130Q), with uncertain effects on adiposity. This study explored the functional role of rs20541 on adipocyte biology and its association with obesity-related parameters in Malaysian adults. In vitro, 3T3-L1 mouse adipocytes (ATCC® CL-173™) were treated with IL-13 rs20541 wild-type (R130) or variant (Q130) recombinant proteins. Adipogenesis, lipolysis, glucose uptake and whole transcriptomic sequencing (WTS -Mus Musculus GRCm39) were assessed. In parallel, a cross-sectional study (May 2023 - October 2024) at Sunway College and Sunway University included anthropometry cardiometabolic assessment and KASP genotyping. Genotype distributions were analyzed under allelic (A vs G), dominant (GG+GA vs AA) and recessive (AA+AG vs GG) models. Overall, Q130-treated adipocytes exhibited higher glucose uptake [basal: 8.68 vs. 6.10 vs. 5.85 μ M and insulin stimulation: 39.68 vs. 25.69 vs. 24.65 μ M; $p < 0.05$] but reduced lipolysis [basal: 1.97 vs. 2.05 vs. 2.13 nmol and isoproterenol-stimulated: 2.57 vs. 4.28 vs. 5.58 nmol; $p < 0.05$]. WTS revealed upregulation of Ucp1, Ucp3 and Scd1 (thermogenesis, fatty acid metabolism, PPAR/AMPK pathways) and downregulation of Fasn, Il6 and Tnf (lipogenesis, inflammatory signalling). KEGG analysis (adj-p < 0.05) identified 15 altered pathways spanning lipid metabolism, glucose/insulin signalling and inflammation. In the cohort (n=397; mean age: 21.5 \pm 3.5 years), A allele frequency was 28.2% (AA 11.6%, AG 33.2%, GG 55.2%). AA carriers (dominant model) had higher waist-to-hip ratio (WHR) (0.82 vs. 0.79; adj-p = 0.028) while A carriers (recessive model) had lower WHR (0.78 vs. 0.81; adj-p = 0.050) but higher fasting glucose (5.10 vs. 4.90 mmol/L; adj-p = 0.012). In conclusion, IL-13 rs20541 Q130 influences adipocyte metabolism and associates with obesity-related traits, supporting its potential as a marker for obesity risk and precision

Keywords: Obesity, IL-13, rs20541, Adipocyte Biology, Genotype-Phenotype