



Title	Implication of the obesity-associated genetic variants identified from recent genome-wide association studies in Hong Kong Chinese
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APPL1 antagonises Tribble 3 in regulating hepatic glucose production through fine-tuning insulin-evoked Akt signalling

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Background: Insulin inhibits hepatic glucose production through activation of Akt signalling cascades. Hepatic insulin resistance contributes to both fasting and fed hyperglycaemia in patients with type 2 diabetes. Our previous study demonstrated that APPL1 is a key player in mediating the glucose-lowering effects of insulin. The major objective of this study was to further characterise how APPL1 modulates insulin-mediated inhibitory effects on glucose production using both ex-vivo experiments and mouse models.

Methods: Primary rat hepatocytes were infected with adenovirus expressing full-length APPL1 or APPL1-specific RNAi or Tribble-3 (TRB3) for 24 hours, followed by starvation for 24 hours, and then treated with insulin (10 nM) for various time-points. Total cell lysate was subjected to co-immunoprecipitation, immunoblotting, real-time PCR analysis. Discontinuous sucrose-gradient ultracentrifugation was employed to separate the mouse liver into cytosolic, plasma membrane and endosomal fractions.

Results: In primary rat hepatocytes, adenovirus-mediated overexpression of TRB3 attenuated insulin-induced phosphorylation of Akt and suppression of the gluconeogenic program, but these effects were reversed by APPL1 overexpression. Western blot analysis revealed that the expression of TRB3 is markedly increased in the liver of db/db diabetic mice. TRB3 caused insulin resistance and diabetes by trapping and inactivating Akt. On the other hand, overexpression of APPL1 counteracted the detrimental effects of TRB3 on suppression of insulin-evoked Akt activation, resulting in improved insulin sensitivity. Subcellular fractionation analysis revealed that both Akt and APPL1, but not TRB3, were translocated from cytosol to the plasma membrane and the endosomes upon insulin stimulation. In addition, insulin-stimulated Akt translocation was significantly enhanced by APPL1 overexpression, but attenuated by APPL1 knockdown.

Conclusions: APPL1 and TRB3 serve as a pair of 'Yin-and-Yang' molecules that tightly control the blood glucose levels through fine-tuning insulin-evoked Akt signalling.

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Implication of the obesity-associated genetic variants identified from recent genome-wide association studies in Hong Kong Chinese

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Introduction: Recently, two large-scale genome-wide association (GWA) studies by Thorleifsson et al and Willer et al had identified several novel loci associated with obesity and/or body mass index (BMI). This project aimed to examine these loci for associations with obesity in the Hong Kong Chinese population.

Methods: We investigated 13 genetic loci previously reported to be associated with obesity and/or BMI in a case-control study involving 470 obese cases (BMI ≥ 27.5) and 700 normal-weight control ($18.5 \leq \text{BMI} \leq 23.0$). rs8050136, rs10938397, and rs17782313, which showed most significant associations with obesity in the case-control study, were further studied in the population-based Hong Kong Cardiovascular Risk Factors Prevalence Study (CRISPS) cohort.

Results: Seven single nucleotide polymorphisms (SNPs) showed statistically significant associations with obesity in the case-control cohort ($P_{\text{one-tailed}} < 0.05$). These included *GNPDA2* rs10938397; *FTO* rs8050136; *MC4R* rs17782313; *KCTD15* rs29941; *SFRS10-ETV5-DGKG* rs7647305; *SEC16B-RASAL2* rs10913469; and *NEGR1* rs3101336. The combined genetic risk of these seven obesity-associated SNPs was analysed and we observed an increased risk of obesity by 1.36 times for each additional risk allele. In the extension study, rs8050136, rs10938397 and rs17782313 also showed significant associations with BMI.

Conclusion: We have successfully replicated the associations of seven SNPs reported in recent GWA studies with obesity in a Hong Kong Chinese population.

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