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POSTER PRESENTATION – P31

AN ADAPTIVE VARIANT OF SLC25A11 ENHANCES BROWN ADIPOSE TISSUE ACTIVITY IN HUMANS

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Background: Brown adipose tissue (BAT) counteracts obesity primarily by enhancing energy expenditure. Although substantial individual variation in BAT activity suggests the involvement of genetic factors, reports on specific genetic variants remain limited.

Objective: To identify genetic determinants of human BAT activity by integrating adipose tissue eQTL data and natural selection metrics for genes differentially expressed between BAT and WAT.

Methods: In this study, we screened 119 genes previously identified as differentially expressed between BAT and white adipose tissue (WAT) by Perdikari et al., integrating expression quantitative trait loci (eQTL) data in adult adipose tissue with natural selection intensity metrics.

Results: Consequently, we identified SLC25A11, a component of the malateaspartate shuttle (MAS), as a novel BAT-associated molecule. Genetic variants in SLC25A11 were significantly associated with high BAT activity in 444 adults who underwent PET-CT imaging following cold exposure. A consistent trend was also observed via infrared thermography in an independent adult cohort. In silico mining revealed that these genetic variants upregulate SLC25A11 expression in adipose tissue and correlate with a reduced risk of obesity and type 2 diabetes. Furthermore, evolutionary analysis using modern and ancient human genomic diversity panels demonstrated that this genetic variant, linked to high BAT activity, rapidly spread through ancient European populations via positive natural selection during the Last Glacial Maximum to Heinrich Event 1. Notably, it was revealed that this positive natural selection ceased to operate after Heinrich Event 1.

Conclusion: These findings underscore the critical role of the MAS in regulating BAT thermogenesis and support the hypothesis that environmental adaptations experienced by ancestral populations have shaped obesity susceptibility in modern humans.

Keywords: Cold adaptation; Brown adipose tissues; SLC25A11; Positive natural selection.

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