

## PHENOTYPIC CONSEQUENCES AND EVOLUTION OF THE GHRELIN O-ACYL TRANSFERASE GENE VARIATION IN HUMANS

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Ghrelin is a gut-derived peptide hormone regulating various nervous and metabolic functions in mammals and the only known protein to require post-translational octanoylation for the activity. Ghrelin O-acyl transferase (GOAT) was recently identified as an enzyme that catalyzes the octanoylation of ghrelin. We tested associations between single nucleotide polymorphisms (SNP) near the human GOAT gene (*GOAT*) and various metabolic parameters in modern humans. We found that an intergenic SNP located in the 3' downstream of the *GOAT* was significantly associated with the heart rate and the systolic blood pressure in 570 Japanese individuals ( $P < 0.05$ ). The associations were successfully replicated in an independent cohort comprising 642 Japanese individuals ( $P < 0.05$ ). Moreover, population genetic analyses on the polymorphism pattern around the *GOAT* detected signs of recent positive selection in populations with European ancestry. Ghrelin is known to show cardiovascular protective effects in addition to secretion of growth hormone, stimulation of feeding and adiposity. The present results suggest that the *GOAT* influences blood pressure in humans, likely through modulating the cardiovascular protective effects of ghrelin, and furthermore, the genetic variation possibly play a role in the adaptive dispersal of ancient Europeans.

Keywords: Ghrelin O-acyl transferase, single nucleotide polymorphism, natural selection, humans