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Rare genetic coding variants associated with human longevity and protection against age-related diseases

Jhih-Rong Lin, Patrick Sin-Chan, [...]Zhengdong D. Zhang

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Abstract

Extreme longevity in humans has a strong genetic component, but whether this involves genetic variation in the same longevity pathways as found in model organisms is unclear. Using whole-exome sequences of a large cohort of Ashkenazi Jewish centenarians to examine enrichment for rare coding variants, we found most longevity-associated rare coding variants converge upon conserved insulin/insulin-like growth factor 1 signaling and AMP-activating protein kinase signaling pathways. Centenarians have a number of pathogenic rare coding variants similar to control individuals, suggesting that rare variants detected in the conserved longevity pathways are protective against age-related pathology. Indeed, we detected a pro-longevity effect of rare coding variants in the Wnt signaling pathway on individuals harboring the known common risk allele APOE4. The genetic component of extreme human longevity constitutes, at least in part, rare coding variants in pathways that protect against aging, including those that control longevity in model organisms.