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The genomic basis of human lifespan

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Motivation and Aim: Whilst of great interest to us all, investigation into the genomic basis of longevity has been hampered by limited sample sizes. As a result, until very recently, only 4 genome-wide significant loci had been discovered and replicated, limiting the inferences that be made about its genetic basis [1].

Results: Here using an independent replication cohort, we examine 20 published [2] but unreplicated genome-wide significant loci for longevity, validating associations at or near CDKN2B-AS1, ATXN2/BRAP, FURIN/FES, FOXO3A, 5q33.3/EBF1, ZW10, PSORS1C3, 13q21.31, and provide evidence against previous findings near CLU, CHRNA4, PROX2, and d3-GHR. In a GWAS using all data combined, totalling over 1m lifespans, we next find 15 further loci at genome-wide significance. Of the life lengthening loci significant in our analyses, we find many protect against cardiovascular, glycaemic and neurological diseases (CGND), but not cancer. Using our GWAS, we then create polygenic scores for survival in independent sub-cohorts, and are able to partition populations, using DNA alone, into deciles of expectation of life, with a difference in excess of five years from top to bottom decile.

Conclusion: It seems that natural selection has been more effective in purging common variants affecting lifespan through cancer, but in our modern obesogenic and long lived environment has yet to as effectively purge variants affecting CGND. Materially accurate predictions of lifespan can now be made from DNA.

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