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Retesting the influences of mutation accumulation and antagonistic pleiotropy on human senescence and disease

Erping Long[1,2] and Jianzhi Zhang[1]*

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Multiple hypotheses have been proposed to explain the origin of senescence, which refers to the gradual deterioration of functional characteristics with ageing[1]. Two of the leading hypotheses are mutation accumulation (MA)[2] and antagonistic pleiotropy (AP)[3]. The MA hypothesis states that natural selection is ineffective in purging mutations that cause senescence as these mutations have little fitness consequence due to the absence of phenotypic effects until after the reproductive age. The related AP hypothesis asserts that these mutations may even be selectively favoured because they promote growth or reproduction owing to their pleiotropic effects. By examining genetic variants associated with diseases that appear at different life stages, Rodríguez and colleagues claimed to have found genomic evidence for these two hypotheses in humans[4]. Our further analyses of their data, however, show that their results are not robust and their conclusions unsupported.

In testing the MA hypothesis, Rodríguez et al. took advantage of published genome-wide association studies and analysed 104 single nucleotide polymorphisms (SNPs) associated with 46 diseases. They reported that risk allele frequencies (RAFs) are significantly higher for the SNPs associated with late-onset diseases than for those associated with early-onset diseases when the threshold between early and late onset is placed anywhere at or before the age of 40 yr (fig. 1a in Rodríguez et al.[4])—a trend predicted by the MA hypothesis under the assumption of mutation–selection balance[5]. However, this trend disappears (Fig. 1a) following the removal of only one disease: acute lymphoblastic leukaemia (ALL), which has an onset age of 1 yr and is associated with nine SNPs with exceptionally low RAFs (all <0.06, compared with the mean RAF of 0.31 in the entire dataset). Rodríguez et al. further showed that the mean genetic variance explained by disease-associated SNPs is significantly

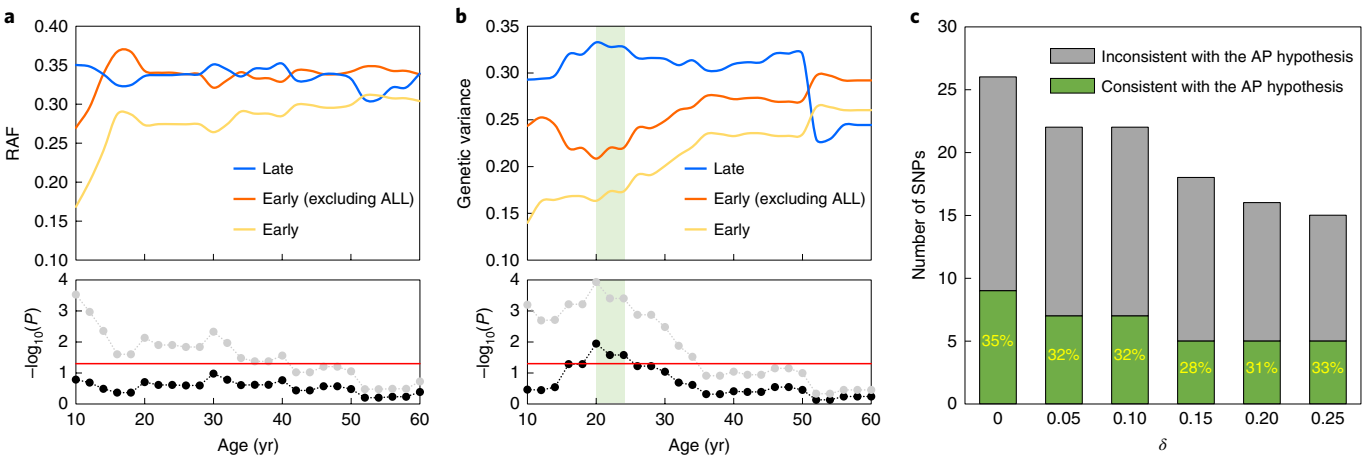

Fig. 1 | Retesting the influences of MA and AP on human senescence and disease. a, Mean RAFs for SNPs associated with early- or late-onset diseases as a function of the age threshold between these two groups of diseases. The result for early-onset diseases following the removal of ALL is also shown. Grey dots depict the $-\log_{10}(P)$ at each age threshold for the whole dataset (Wilcoxon one-tailed test), whereas black dots depict the corresponding values following the removal of ALL. The red horizontal line shows $-\log_{10}(0.05)$. **b**, The same as **a**, but showing the mean genetic variance explained by the SNPs in each group of diseases. Following the removal of ALL, significant differences are observed only for thresholds at 20, 22 or 24 yr (green shading), and they disappear after correction for multiple testing. **c**, Number (and percentage) of SNPs consistent or inconsistent with the AP theory as a function of the minimal difference (δ) between the frequencies of the two alternative alleles at each SNP. All analyses followed Rodríguez et al.[4] unless otherwise mentioned. Panels **a** and **b** are drawn in the same fashion as Fig. 1a,b in Rodríguez et al.[4] for easy comparison.

[1]Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, MI, USA. [2]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. *e-mail: jianzhi@umich.edu

greater for late-onset diseases than for early-onset diseases when the age threshold is placed at or before 36 yr (fig. 1b in Rodríguez et al.[4]). But, when ALL is excluded, the above difference vanishes almost entirely; only when the age threshold is set at 20, 22 or 24 yr is there a significant difference (Fig. 1b). Because this observation is difficult to interpret and the statistical significance does not hold after the correction for multiple testing, the age-related difference is unlikely to be genuine. Rodríguez et al. would have found these problems if they had investigated the robustness of their results by bootstrapping the diseases[6]. Regardless, their findings seem idiosyncratic and their evidence for the MA hypothesis is not robust.

Rodríguez et al. compiled SNPs that are each associated with two diseases to test the AP hypothesis. They then divided these SNPs into four groups on the basis of whether the same allele of a SNP (or two strongly linked alleles at two SNPs) increases the risks of both diseases and whether the two diseases occur in the same life stage. Using a 2×2 table, they found a significant excess of SNPs (26 in total) for which the two alternative alleles respectively increase the risk of one early-onset and one late-onset disease (fig. 1c in Rodríguez et al.[4]), which they interpreted as evidence for the AP hypothesis. However, the key prediction of the AP hypothesis is that the risk allele for the early-onset disease (which is also the protective allele for the late-onset disease) is selected against relative to the alternative allele at the SNP. That is, under the mutation–selection balance, the AP hypothesis predicts a lower RAF for the early-onset disease than for the late-onset disease for each of these 26 SNPs. To verify this prediction, we examined the CEU population genomic data from Phase 1 of the 1000 Genomes Project[7]. As shown in Fig. 1c, only 35% of the 26 SNPs are consistent with the AP hypothesis. To examine the robustness of this finding, we limited the analysis to the subset of 26 SNPs for which the RAFs for the two diseases differ by at least $\delta = 0.05$, 0.10, 0.15, 0.20 or 0.25, respectively. We found that in all cases only 28% to 35% of the SNPs are consistent with the AP hypothesis (Fig. 1c). Although none of these percentages are significantly lower than the chance expectation of 50% ($P > 0.05$, binomial test followed by multiple testing correction) that would allow the rejection of the AP hypothesis, there is also no evidence for the AP hypothesis.

We note that the above tests of the MA and AP hypotheses rely on the assumption that the mutational supply of deleterious alleles at a SNP is counterbalanced by the selective purge of such alleles. Neither hypothesis could be tested in this fashion when the mutation–selection balance is violated, which can occur where there are recent demographic or environmental changes[8], for example. In summary, our reanalysis of the dataset of Rodríguez et al. found no evidence for the MA or AP hypothesis. More studies are needed to further test the influences of MA and AP in human senescence and age-related disease. As the fitness effect varies greatly among diseases and disease subtypes, and because the mutation–selection balance may not hold for all disease alleles, it is necessary to consider these factors in future studies. With the rapid progress of medical genomics, sufficiently large datasets may soon be available to permit robust tests of various evolutionary hypotheses of senescence—a subject that is increasingly important due to the disproportional expansions of our ageing populations over time[9].

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Author contributions

E.L. and J.Z. designed the tests and wrote the paper; E.L. analyzed the data.

Competing interests

The authors declare no competing interests.

Additional information

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