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Evolutionary demographic models reveal the strength of purifying selection on susceptibility alleles to late-onset diseases

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1 Assessing the role played by purifying selection on a Susceptibility Allele to Late-Onset Disease (SALOD) is crucial to understand the puzzling allelic spectrum of a disease: most alleles are recent and rare. This fact is surprising, as it suggests that alleles are under purifying selection, while alleles that are involved in post-menopause mortality are often considered neutral in the genetic literature. The aim of this presentation is to use an evolutionary demography model in order to assess the magnitude of selection on SALODs while accounting for epidemiological and sociocultural factors. We develop an age-structured population model allowing for the calculation of SALODs' selection coefficients (i) for a large and realistic parameter space for disease onset, (ii) in a two-sex model in which men can reproduce at old age, and (iii) for situations in which child survival depends on maternal, paternal and grandmother care. The results show that SALODs are under purifying selection for most known age-at-onset distributions of late-onset genetic diseases. Estimates regarding various genes involved in susceptibility to cancer or Huntington disease demonstrate that negative selection largely overcomes the effects of drift in most human populations. This is also likely true for neurodegenerative or polycystic kidney diseases, although sociocultural factors modulate the effect of selection in these cases. We conclude that neutrality is probably the exception among alleles that have a deleterious effect at old age and that accounting for sociocultural factors is required to understand the full extent of the force of selection shaping senescence in humans.

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