

Exploring differences in LD levels between lifespan-related loci

Ilya Y. Zhbannikov, Anatoliy I. Yashin

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Project Summary

This is a scientific application that was developed in order to explore differences in Linkage Disequilibrium (LD) effects between lifespan-related loci.

The roles of genetic and non-genetic factors in aging and longevity-related traits are intensively studied during last decades. However, many results of these studies remain non-replicated in studies of independent populations. The purpose of this project (and corresponding application) is to investigate the role of LD in modulating estimated effects of genetic variants on longevity.

Method

We considered the two SNP loci associated with lifespan in the absence of Linkage Disequilibrium (LD) and investigated how different levels of LD between these loci influence association of the minor allele in the first locus with lifespan in hypothetical study populations with the same initial frequencies of minor alleles and mortality risks for carriers of each of four genotypes in these loci.

Description of variables and assumptions:

Main panel

We consider two loci, $V_1 = (0, 1)$ and $V_2 = (0, 1)$, where the notation “0” corresponds major- and “1” - to minor allele.

Let t be the time, in years, describes a person’s age.

Proportion hazard section

$m_1(t)$, $m_2(t)$ - are the frequencies of the minor allele in locus 1 and 2, respectively.

$m_{00}(t)$, $m_{10}(t)$, $m_{01}(t)$, $m_{11}(t)$ - genotype frequencies

m_{00} , m_{10} , m_{01} , m_{11} - initial values of genotype frequencies of genotypes, which values can be set using the sliders under the “Proportion hazard” section.

If the checkbox “Freeze P1, P2” is set, then only m_{11} can be adjusted, and m_{00} , m_{10} , m_{01} are calculated based on the value of m_{11} .

Mortality section

Denote $\mu_{ij}(t)$ to be the mortality risk for each genotype (“00”, “01”, “10”, “11”).

Denote $\mu_{00}(t)$ to be the mortality risk for the genotype of “00”. Initial value for the $\mu_{00}(t)$ can be set using corresponding slider under the “Mortality” section.

Other mortality risks corresponding to other genotypes (“01”, “10”, “11”) can be calculated from the following equations:

First model:

$$\begin{aligned}\mu_{10} &= \mu_{00}(1 + D_1) \\ \mu_{01} &= \mu_{00}(1 + D_2) \\ \mu_{11} &= \mu_{00}(1 + D_1 + D_2)\end{aligned}$$

Where D_1 , D_2 are the increments to genotype's relative risks associated with the presence of minor alleles in the first and in the second loci, respectively.

Second model:

$$\begin{aligned}\mu_{10} &= \mu_{00}H_1 \\ \mu_{01} &= \mu_{00}H_2 \\ \mu_{11} &= \mu_{00}H_1H_2\end{aligned}$$

Where H_1 , H_2 are relative risks of genotypes (1,0) and (0,1) with respect to genotype (0,0) and H_1H_2 is relative risk of genotypes (1,1) with respect to genotype (0,0).

The choice between the two models can be made using corresponding checkbox " D_1, D_2 ".

Gompertz effects

If the checkbox "Gompertz" is checked, then the mortalities are calculated with the following equations:

For the first model:

$$\begin{aligned}\mu_{00} &= a \cdot e^{b \cdot t} \\ \mu_{10} &= \mu_{00}H_1 \\ \mu_{01} &= \mu_{00}H_2 \\ \mu_{11} &= \mu_{00}H_1H_2\end{aligned}$$

For the second model:

$$\begin{aligned}\mu_{00} &= a \cdot e^{b \cdot t} \\ \mu_{10} &= \mu_{00}(1 + D_1) \\ \mu_{01} &= \mu_{00}(1 + D_2) \\ \mu_{11} &= \mu_{00}(1 + D_1 + D_2)\end{aligned}$$

Where a and b can be set from corresponding slider inputs.

Natural logarithm

If the checkbox "Log" is set, then the natural logarithm is applied to mortality functions.

Main Plots panel ("Main Plots")

$m_1(t)$, $m_2(t)$ - are the frequencies of the minor alleles in locus 1 and 2 respectively.

$D(t)$, $r^2(t)$ - Linkage Disequilibrium between these two loci, written in forms of D and r^2 .

$S(t)$ - Survival function for the population.

$m_{ij}(t)$ - are the frequencies of the minor allele in locus 1 and 2, respectively.

Button "Save" saves the plots as a .png image.

If the checkbox "No title" is set, then figures are saved without titles.

Mortality plots panel (“Mortality”)

Plot $\mu_1(t), \mu_0(t)$ shows mortality changes overtime for locus 1 and 2 respectively. Also this panel shows plot for haplotype mortalities ($\mu_{00}(t), \mu_{01}(t), \mu_{10}(t), \mu_{11}(t)$)

Button “Save” saves the plots as a .png image. Is the checkbox “No title” is set, then the figures are saved without titles.

Minor allele frequencies panel (“MAF”)

This panel shows the plot for minor allele frequencies of haplotypes: $m_{00}, m_{10}, m_{01}, m_{11}$. Button “Save” saves the plot as a .png image. Is the checkbox “No title” is set, then the figure is saved without title.

Linkage disequilibrium panel (“LD”)

This panel shows the plot for the linkage disequilibrium between two loci: D and its variation, r^2 . Button “Save” saves the plot as a .png image. Is the checkbox “No title” is set, then the figure is saved without title.