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The impact of recent population history on the deleterious mutation load in humans and close evolutionary relatives

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Over the past decade, there has been both great interest and confusion about whether recent demographic events — notably the Out-of-Africa-bottleneck and recent population growth — have led to differences in mutation load among human populations. The confusion can be traced to the use of different summary statistics to measure load, which lead to apparently conflicting results. We argue, however, that when statistics more directly related to load are used, the results of different studies and data sets consistently reveal little or no difference in the load of non-synonymous mutations among human populations. Theory helps to understand why no such differences are seen, as well as to predict in what settings they are to be expected. In particular, as predicted by modeling, there is evidence for changes in the load of recessive loss of function mutations in founder and inbred human populations. Also as predicted, eastern subspecies of gorilla, Neanderthals and Denisovans, who are thought to have undergone reductions in population sizes that exceed the human Out-of-Africa bottleneck in duration and severity, show evidence for increased load of non-synonymous mutations (relative to western subspecies of gorillas and modern humans, respectively). A coherent picture is thus starting to emerge about the effects of demographic history on the mutation load in populations of humans and close evolutionary relatives.

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Introduction

The recent demographic history of human populations is reflected in their distributions of genetic variation. For instance, Europeans and Asians harbor a greater fraction of high frequency variants compared to Africans, likely due to an ancient 'Out-of-Africa' bottleneck [1–4], and all of these populations harbor numerous rare variants resulting from more recent explosive growth [4–9]. Genetic variation in human populations has also been affected by founder events [10–12], by inbreeding [13,14••], and by extensive admixture among populations [15,16] and with archaic humans [17,18].

It is therefore natural to ask whether recent demographic events also affected the burden of deleterious mutations, leading it to differ among extant human populations. In addition to the observation that overall patterns of genetic diversity vary among populations with different demographic histories, theory suggests that, at equilibrium, the efficiency with which purifying selection removes deleterious variation is profoundly affected by population size and degree of inbreeding [19••,20–22,23••]. With data now available to address the question, the possibility that there exist differences in the burden of deleterious mutation among human populations has garnered considerable attention.

Answers to this question have been confusing, because many studies appear to reach conflicting conclusions (cf. [24,25,26••]). In trying to sort out the source of the conflicts, we start by reviewing what is meant by the burden of deleterious mutations. Traditionally, this burden has been quantified in terms of the mutation load (sometime abbreviated by load below), defined as the proportional reduction in average fitness due to deleterious mutations [19••,23••,27•,28•,29]. Under a simple model that assumes one, bi-allelic locus with fitnesses 1, 1-hs and 1-s, the load is

$$L = 2pq{\cdot}hs + q^2{\cdot}s,$$

where p and q are the 'normal' and 'deleterious' allele frequencies. This reduces to

$$L = q{\cdot}s \tag{1}$$

in the additive (semi-dominant) case and to

$$L = q^2{\cdot}s \tag{2}$$

in the recessive case. More generally, load takes the form

$$L = \frac{W_{\max} - W_{\text{-}}}{W_{\max}},$$

where $W_{\max}$ is the fitness of a mutation-free individual and $W_{\text{-}}$ is the average fitness. In practice, we cannot measure fitness and we know little about the distribution of selection and dominance coefficients, let alone about

how the effects of deleterious mutations combine across loci. This is why recent studies have relied on population genetic summaries meant as proxies for load.

The choice of proxy turns out to be key in what the studies found. Notably, Lohmueller and colleagues introduced two summaries in order to compare individuals of European and African descent [30••]. Using the first, they found the ratio of non-synonymous to synonymous segregating sites to be greater in the European sample than in the African one, which they interpreted as evidence for a reduced 'efficacy of selection' in Europeans. Using the second summary, they found that European individuals carry (on average) more sites that are homozygous for non-synonymous derived alleles than do Africans, which they took as suggesting that Europeans likely suffer from a greater burden of recessive deleterious non-synonymous mutations. More recently, Simons *et al.* [31••] and Do *et al.* [32••] introduced a third summary (defined slightly differently in the two studies), the average number of derived non-synonymous variants per individual. They found no significant differences between European and African populations, and interpreted the pattern as indicating little or no difference in load. These studies and others [4,10,11,33–42] applied the same methodologies to subsets of non-synonymous variants classified according to their predicted severity (e.g., using computational tools that rely on phylogenetic conservation and protein structure [43]), as well as to other human populations (see also [44,45]). With few exceptions (see below), analyses relying on the Lohmueller *et al.* summaries found substantial differences among populations whereas those that relied on the Simons *et al.* and Do *et al.* summaries did not.

Comparing proxies for load

Given that the answer seems to depend on the summary, the question becomes which summary is most appropriate. The ideal summary would relate to load as directly as possible but also be insensitive to other differences among populations.

With these criteria in mind, we first consider the ratio of the number of non-synonymous to synonymous sites segregating in a population sample, P_N/P_S (or subsets of non-synonymous sites). The idea is that P_S measures neutral diversity levels, and therefore P_N/P_S measures an effective proportion of neutral non-synonymous mutations [46]; increased P_N/P_S then reflects relaxed selection on non-synonymous mutations [25,30••]. This interpretation applies at demographic equilibrium, for example, when the population size is constant, or when non-synonymous mutations are either neutral or strongly selected, but it breaks down when neither assumption holds, which is precisely the case of interest. Under a population bottleneck, for example, P_N/P_S first exhibit drastic changes because increased drift affects P_N and P_S differently, due to the different initial nonsynonymous and synonymous frequency spectra [30••,32••]; then P_N and P_S approach equilibrium at different rates because selected alleles have faster turnover than neutral ones [26••,31••,47,48]. Neither of these effects is related to relaxation of selection or increased load. To complicate the interpretation of P_N/P_S even further, this statistic is extremely sensitive to the sample size (again because of the different synonymous and nonsynonymous frequency spectra). As a result, changes to P_N/P_S do not correspond to changes to load in any obvious way, even under straightforward demographic scenarios and assumptions about selection (Figure 1a and [24]).

We next consider the behavior of the average number of homozygous derived non-synonymous sites. For recessive deleterious mutations, individual load is related directly to this number (cf. Eq. (2)). However, not all mutations that contribute to this summary are recessive or deleterious. Notably, many derived non-synonymous alleles may be neutral, and because they reach higher frequencies than deleterious ones, they would contribute disproportionally to the number of homozygous, derived sites, swamping any underlying signal. Moreover, demographic events often have marked effects on the number of neutral derived homozygous sites (Figure 1b). For instance, bottlenecks increase the variance of neutral allele frequencies, $V(p^2) = E(p^2) - E^2(p)$, without affecting their mean, $E(p)$, thus increasing the frequency of homozygotes, $E(p^2)$. Comparing European populations that experienced the Out-of-Africa bottleneck to African ones that have not, we would therefore expect a large excess of homozygous, derived neutral sites in Europeans, even in the absence of a difference in load. Restricting the analysis to subsets of variants that are predicted to be more damaging will not solve this problem: while such subsets will include fewer neutral alleles, those neutral alleles that remain will contribute proportionally more homozygous sites, because more damaging variants have lower average frequencies [31••]. Moreover, even if considering more damaging classes of variants helps to weed out neutral variants, non-recessive, deleterious variants continue to contribute, again complicating the relationship between the number of homozygous sites and load (Figure 1b). Thus, the utility of this summary is severely compromised by its sensitivity to factors that have little to do with load.

Lastly, we consider the average number of non-synonymous derived alleles. This number is directly related to individual load when derived alleles are deleterious and additive (i.e., semi-dominant) (Equation 1 and Figure 1c). Moreover, for this summary, comparisons between populations are not confounded by the presence of neutral alleles [31••,32••]. This advantage becomes clear by considering a single sample from each population at a non-recombining locus (Figure 2): if the mutation rate on