Title: Genetic costs of domestication and improvement

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ABSTRACT

The ‘cost of domestication’ hypothesis posits that the process of domesticating wild species increases genetic load by increasing the number, frequency, and/or proportion of deleterious genetic variants in domesticated genomes. This cost may limit the efficacy of selection and thus reduce genetic gains in breeding programs for these species. Understanding when and how genetic load evolves can also provide insight into fundamental questions about the interplay of demographic and evolutionary dynamics. Here we describe the evolutionary forces that may contribute to genetic load during domestication and improvement, and review the available evidence for ‘the cost of domestication’ in animal and plant genomes. We identify gaps and explore opportunities in this emerging field, and finally offer suggestions for researchers and breeders interested in addressing genetic load in domesticated species.

Keywords: genetic load, deleterious mutations, crops, domesticated animals

INTRODUCTION

Recently, we have seen a resurgence of evolutionary thinking applied to domesticated plants and animals (e.g. Walsh 2007; Wang *et al*. 2014; Gaut, Díez, and Morrell 2015; Kono *et al*. 2016). One particular wave of this resurgence proposes a general 'cost of domestication': that the evolutionary processes experienced by lineages during domestication are likely to have increased genetic load. This 'cost' was first hypothesized by Lu *et al*. (2006), who found an increase in nonsynonymous substitutions, particularly radical amino acid changes, in domesticated compared to wild lineages of rice. These putatively deleterious mutations were negatively correlated with recombination rate, which the authors interpreted as evidence that these mutations hitchhiked along with the targets of artificial selection (Figure 1B). Lu *et al*. (2006) conclude that: "The reduction in fitness, or the genetic cost of domestication, is a general phenomenon." Here we address this claim by examining the evidence that has emerged in the last decade on genetic load in domesticated species.

The processes of domestication and improvement potentially impose a number of evolutionary forces on populations (Box 1), starting with mutational effects. New mutations can have a range of effects on fitness, from lethal to beneficial. Deleterious variants constitute the mostly directly observable, and likely the most important, source of genetic load in a population. The shape of the distribution of fitness effects of new mutations is difficult to estimate, but theory predicts that a large proportion of new mutations, particularly those that occur in coding portions of the genome, will be deleterious at least in some proportion of the environments that a species occupies (Ohta 1972; 1992; Gillespie 1994). These predictions are supported by experimental responses to artificial selection and mutation accumulation experiments, and molecular genetic studies (discussed in Keightley and Lynch 2003).

The rate of new mutations in eukaryotes varies, but is likely at least 1×10^{-8} / base pair / generation (Baer, Miyamoto, and Denver 2007). For the average

eukaryotic genome, individuals should thereby be expected to carry a small number of new mutations not present in the parent genome(s) (Agrawal and Whitlock 2012). The realized distribution of fitness effects for these mutations will be influenced by inbreeding and by effective population size (Figure 2A; Gillespie 1999; Whitlock 2000; Arunkumar *et al*. 2015; Keightley and Eyre-Walker 2007). Generally, for a given distribution of fitness effects for new mutations, we expect to observe relatively fewer strongly deleterious variants and more weakly deleterious variants in smaller populations and in populations with higher rates of inbreeding (Figure 2A).

Domestication and improvement often involve increased inbreeding. Allard (1999) pointed out that many important early cultigens were inbreeding, with inbred lines offering morphologically consistency in the crop. In some cases, domestication came with a switch in mating system from highly outcrossing to highly selfing (e.g. in rice; Kovach, Sweeney, and McCouch 2007). The practice of producing inbred lines, often through single-seed descent, with the specific intent to reduce heterozygosity and create genetically 'stable' varieties, remains a major activity in plant breeding programs. Reduced effective population sizes (N_e) during domestication and improvement and artificial selection on favorable traits also constitute forms of inbreeding (Figure 1). Even in species without the capacity to self-fertilize, inbreeding that results from selection can dramatically change the genomic landscape. For example, the first sequenced dog genome, from a female boxer, is 62% homozygous haplotype blocks, with an N50 length of 6.9 Mb (versus heterozygous region N50 length 1.1 Mb; Lindblad-Tor *et al*. 2005). This level of homozygosity drastically reduces the effective recombination rate, as crossover events will essentially be switching identical chromosomal segments. The likelihood of a beneficial allele moving into a genomic background with fewer linked deleterious alleles is thus reduced.

Linked selection, or interference among mutations, has much the same effect. For a trait influenced by multiple loci, interference between linked loci can limit

the response to selection (Hill and Robertson 1966). Deleterious variants are more numerous than those that have a positive effect on a trait and thus should constitute a major limitation in responding to selection (Felsenstein 1974). This forces selection to act on the net effect of favorable and unfavorable mutations in linkage (Figure 1B). As inbreeding increases, selection is less effective at purging moderately deleterious mutations and new slightly beneficial mutations more likely to be lost by genetic drift, which will shift the distribution of fitness effects for segregating variants and result in greater accumulation of genetic load over time (Figure 2A–C).

Overall, the cost of domestication hypothesis posits that compared to their wild relatives domesticated lineages will have:

1. Deleterious variants at higher frequency, number, and proportion
2. Enrichment of deleterious variants in linkage disequilibrium with loci subject to strong, positive, artificial selection

With domestications, these effects may differ between lineages that experienced domestication followed by modern improvement (e.g. ‘elite’ varieties and commercial breeds) and those that experienced domestication only (e.g. landraces and non-commercial populations). Generally speaking, the process of domestication is characterized by a genetic bottleneck followed by a long period of relatively weak and possibly varying selection, while during the process of improvement, intense selection over short time periods is coupled with limited recombination and an additional reduction in N_e, often followed by rapid population expansion (Figure 1A; Yamasaki, Wright, and McMullen 2007). Gaut, Díez, and Morrell (2015) propose that elite crop lines should harbor a lower proportion of deleterious variants relative to landraces due to strong selection for yield during improvement, but the opposing pattern could be driven by increased genetic drift due to limited recombination, lower N_e, and rapid population expansion. At least one study shows little difference in genetics load between landrace and elite lines in sunflower (Renaut and Rieseberg 2015). It is likely that

relative influence of these factors varies dramatically across domesticated systems.

<u>Box 1. Domesticated lineages may experience:</u>

- **Reduced efficacy of selection:**
  - Deleterious variants that are in linkage disequilibrium with a target of artificial selection can rise to high frequency through genetic hitchhiking, as long as the their fitness effects are smaller than the effect of the targeted variant (Figure 1B).
  - Domesticated lineages can experience reduced effective recombination rate as inbreeding increases and heterozygosity drops (Figure 1B). Increased linkage disequilibrium allows larger portions of the genome to hitchhike, and negative linkage disequilibrium across advantageous alleles on different haplotypes can cause selection interference (Felsenstein 1974).
  - The loss of allelic diversity through artificial selection, genetic drift, and inbreeding (Figure 1B) can reduce trait variance (Eyre-Walker, Woolfit, and Phelps 2006), which reduces the efficacy of selection.
  - **However**: any significant increase in inbreeding, particularly the transition from outcrossing to selfing, **allows selection to more efficiently purge recessive, highly deleterious alleles**, as these alleles are exposed in homozygous genotypes more frequently (Arunkumar *et al*. 2015). This shifts the more deleterious end of the distribution of fitness effects for segregating variants towards neutrality (Figure 2A).

- **Increased genetic drift:**
  - Domestication involves one or more genetic bottlenecks (Figure 1A), where N_e is reduced. In smaller populations, genetic drift is stronger relative to the strength of selection, and deleterious variants can reach higher frequencies.

166 ○ N_e varies across the genome (Charlesworth 2009). In particular,
167 when regions surrounding loci under strong selection (e.g.
168 domestication QTL) rapidly rise to high frequency, the N_e for that
169 haplotype rapidly drops, and so drift has a relatively stronger effect
170 in that region.
171 ○ The rapid population expansion coupled with long-distance
172 migration typical of many domesticated lineages' demographic
173 histories can result in the accumulation of deleterious genetic
174 variation known as 'expansion load' (Peischl *et al*. 2013;
175 Lohmueller 2014). This occurs when serial bottlenecks are followed
176 by large population expansions (e.g., large local carrying
177 capacities, large selection coefficients, long distance dispersal;
178 Peischl *et al*. 2013). This phenomenon is due to the accumulation
179 of new deleterious mutations at the 'wave front' of expanding
180 populations, which then rise to high frequency via drift regardless of
181 their fitness effects (i.e. 'gene surfing', or 'allelic surfing' Klopfstein,
182 Currat, and Excoffier 2006; Travis *et al*. 2007).
183
184 • **Increased mutation load**
185 ○ Domesticated and wild lineages may differ in basal mutation rate,
186 although it is unclear if we would expect this to be biased towards
187 higher rates in domesticated lineages.
188 ○ More likely, deleterious mutations **accumulate** at higher rates in
189 domesticated lineages due to the reduced efficacy of selection.
190 Mutations that would be purged in larger N_e or with higher effective
191 recombination rates are instead retained. This is reflected in a shift
192 in the distribution of fitness effects for segregating variants towards
193 more moderately deleterious alleles (Figure 2A).
194 ○ Smaller population sizes decrease the likelihood of beneficial
195 mutations arising, as these mutations are likely relatively rare and

for a given mutation rate fewer individuals mean fewer opportunities for mutation.

Genetic Load in Domesticated Species

The increasing number of genomic datasets has made the study of genome-wide genetic load increasingly feasible. Since Lu *et al*. (2006) first hypothesized genetic load as a 'cost of domestication' in rice, similar studies have examined evidence for such costs in other crops and domesticated animals.

One approach for estimating genetic load is to compare population genetic parameters between two lineages, in this case domesticated species versus their wild relatives. If domestication comes with the cost of genetic load, we might expect domesticated lineages to have accumulated more nonsynonymous mutations or, if the accumulation of genetic load is due to reduced effective population sizes, to show reduced allelic diversity and effective recombination when compared to their wild relatives. While relatively straightforward, this approach only indirectly addresses genetic load by assuming that: (A) nonsynonymous mutations are on average deleterious, and (B) loss of diversity and reduced recombination indicate a decreased efficacy of selection. This approach also assumes that wild relatives of domesticated species have not themselves experienced population bottlenecks, shifts in mating system, or any of the other processes that could affect genetic load relative to the ancestors.

Another approach for estimating genetic load is to assay the number and proportions of putatively deleterious variants present in populations of domesticated species, using various bioinformatic approaches. This approach directly addresses the question of genetic load, but does not tell us whether the load is the result of domestication or other evolutionary processes (unless wild relatives are also assayed, again assuming that their own evolutionary trajectory

226 has not simultaneously been affected). It also requires accurate, unbiased
227 algorithms for identifying deleterious variants from neutral variants (see below).
228
229 Studies taking these approaches in domesticated species are presented Table 1.
230 We searched the literature using Google Scholar with the terms “genetic load”
231 and “domesticat*”, and in many cases followed references from one study to the
232 next. To the best of our knowledge, the studies in Table 1 represent the majority
233 of the extant literature on this topic. We excluded studies examining only the
234 mitochondrial or other non-recombining portions of the genome. In a few cases
235 where numeric values were not reported, we extracted values from published
236 figures using relative distances as measured in the image analysis program
237 ImageJ (Schneider, Rasband, and Eliceiri 2012), or otherwise extrapolated
238 values from the provided data. Where exact values were not available, we
239 provide estimates. Please note that no one study (or set of genotypes)
240 contributed values to all columns for a particular domestication event, and that in
241 many cases methods used or statistics examined varied across species.
242
243 *Recombination and linkage disequilibrium*
244 The process of domestication may increase recombination rate, as measured in
245 the number of chiasmata per bivalent. Theory predicts that recombination rate
246 should increase during periods of rapid evolutionary change (Otto and Barton
247 1997), and in domesticated species this may be driven by strong selection and
248 limited genetic variation under linkage disequilibrium (Otto and Barton 2001).
249 This is supported by the observation that recombination rates are higher in many
250 domesticated species compared to wild relatives (e.g., chicken, Groenen *et al*.
251 2009; honey bee, Wilfert *et al.* 2007; and a number of cultivated plant species,
252 Ross-Ibarra 2004). In contrast, recombination in some domesticated species is
253 limited by genomic structure (e.g., in barley, where 50% of physical length and
254 many functional genes are in (peri-)centromeric regions with extremely low
255 recombination rates; The International Barley Genome Sequencing Consortium
256 2012), although this structure may be shared with wild relatives. Even when

257 actual recombination rate (chiasmata per bivalent) increases, effective
258 recombination may be reduced in many domesticated species due to an increase
259 in the physical length of fixed or high frequency haplotypes, or linkage
260 disequilibrium (LD). In other words, chromosomes may physically recombine, but
261 if the homologous chromosomes contain identical sequences then no "effective
262 recombination" occurs and the outcome is no different than no recombination. In
263 a striking example, the parametric estimate of recombination rate in maize
264 populations, has decreased by an average of 83% compared to the wild relative
265 teosinte (Wright *et al*. 2005). We note that Mezmouk and Ross-Ibarra (2014)
266 found that in maize deleterious variants are not enriched in areas of low
267 recombination (although see McMullen *et al*. 2009; Rodgers-Melnick *et al*. 2015).
268
269 Strong directional selection like that imposed during domestication and
270 improvement can reduce genetic diversity in long genetic tracts linked to the
271 selected locus (Maynard Smith and Haigh 1974). These regions of extended LD
272 are among the signals used to identify targets of selection and reconstruct the
273 evolutionary history of domesticated species (e.g., Tian, Stevens, and Buckler
274 2009). A shift in mating system from outcrossing to selfing, or an increase in
275 inbreeding, will have the same effect across the entire recombining portion of the
276 genome, as heterozygosity decreases with each generation (Charlesworth 2003).
277 Extended LD has consequences for the efficacy of selection: deleterious variants
278 linked to larger-effect beneficial alleles can no longer recombine away, and
279 beneficial variants that are not in LD with larger-effect beneficial alleles may be
280 lost. We see evidence for this pattern in our review of the literature: LD decays
281 most rapidly in the outcrossing plant species in Table 1 (maize and sunflower),
282 and extends much further in plant species propagated by selfing and in
283 domesticated animals. In all cases where we have data for wild relatives, LD
284 decays more rapidly in wild lineages than in domesticated lineages (Table 1).
285
286 While we primarily report mean LD in Table 1, linkage disequilibrium also varies
287 among varieties and breeds of the same species. For example, in domesticated

288 pig breeds the length of the genome covered by runs of homozygosity ranges
289 from 13.4 to 173.3 Mb, or 0.5–6.5% (Traspov *et al*. 2016). Similarly, among dog
290 breeds average LD decay (to $r^2 \leq 0.2$) ranges from 20 kb to 4.2 Mb (Gray *et al*.
291 2009). In both species, the decay of LD for wild individuals occurs over even
292 shorter distances. This suggests that patterns of LD in these species have been
293 strongly impacted by breed-specific demographic history (i.e., the process of
294 improvement), in addition to the shared process of domestication.
295
296 *Genetic diversity and dN/dS*
297 In the species we present in Table 1, we see consistent loss of genetic diversity
298 when 'improved' or 'breed' genomes are compared to domesticated 'landrace' or
299 'non-commercial' genomes, and again when domesticated genomes are
300 compared to the genomes of wild relatives. This ranges from ~5% nucleotide
301 diversity lost between wolf populations and domesticated dogs (Gray *et al*. 2009)
302 to 77% lost between wild and improved tomato populations (Lin *et al*. 2014). The
303 only case where we see a gain in genetic diversity is in the Andean
304 domestication of the common bean, where gene flow with the more genetically
305 diverse Mesoamerican common bean is likely an explanatory factor (Schmutz *et*
306 *al*. 2013). This pattern is consistent with a broader review of genetic diversity in
307 crop species: Miller and Gross (2011) found that annual crops had lost an
308 average of ~40% of the diversity found in their wild relatives. This same study
309 found that perennial fruit trees had lost an average of ~5% genetic diversity,
310 suggesting that the impact of domestication on genetic diversity is strongly
311 influenced by life history (see also Gaut, Díez, and Morrell 2015). Given a
312 relatively steady evolutionary trajectory for wild populations, loss of genetic
313 diversity in domesticated populations can be attributed to: genetic bottlenecks,
314 increased inbreeding, artificial selection. On an evolutionary timescales, even the
315 oldest domestications occurred quite recently relative to the rate at which new
316 mutations can recover the loss. This is especially true for non-recombining
317 portions of the genome like the mitochondrial genome or non-recombining sex
318 chromosomes. Most modern animal breeding programs are strongly sex-biased,

319 with few male individuals contributing to each generation. In horses, for example,
320 this has likely led to almost complete loss of polymorphism on the Y chromosome
321 via genetic drift (Lippold *et al*. 2011). Loss of allelic diversity can reduce the
322 efficacy of selection by reducing trait variation within species (Eyre-Walker,
323 Woolfit, and Phelps 2006). However, a loss of genetic diversity alone does not
324 necessarily signal a corresponding increase in the frequency or proportion of
325 deleterious variants, and so is not sufficient evidence of genetic load.
326
327 In six of seven species, the domesticated lineage shows an increase in genome-
328 wide nonsynonymous to synonymous substitution rate or number compared to
329 the wild relative lineage (Table 1). The exception is in soybean, where the
330 domesticated *Glycine max* and wild *G. soja* genomes contain approximately the
331 same proportion of nonsynonymous to synonymous single nucleotide
332 polymorphisms (Lam *et al*. 2010). These differences in nonsynonymous
333 substitution rate are likely driven by differences in N_e (Eyre-Walker and Keightley
334 2007; Woolfit 2009). If most nonsynonymous mutations are deleterious, as theory
335 and empirical data suggest, then an increase in nonsynonymous substitutions
336 will reduce mean fitness (Figure 2B-C). The comparisons in Table 1 suggest that
337 this has occurred in domesticated species. This result differs from Moray,
338 Lanfear, and Bromham (2014), who examined rates of mitochondrial genome
339 sequence evolution in domesticated animals and their wild relatives and found no
340 such consistent pattern. This difference may be attributable to the focus of each
341 review (genome-wide versus mitochondria) or, as the authors speculate, to
342 genetic bottlenecks in some of the wild relatives included in their study.
343
344 The ratio of nonsynonymous to synonymous substitutions may not be a good
345 estimate for mutational load. For one, nonsynonymous substitutions are
346 particularly likely to be phenotype changing (Kono *et al*. *bioRxiv*) and contribute
347 to agronomically important phenotypes (Kono *et al*. 2016). Thus artificial
348 selection during domestication and improvement is likely to drive these variants
349 to higher frequencies (or fixation) in domesticated lineages. Thus variants that

350 annotate as deleterious based on sequence conservation (see below), can in
351 some case, contribute to agronomically important phenotypes. In addition,
352 estimates of the proportion of nonsynonymous sites with deleterious effects
353 range from 0.03 (in bacteria; Hughes 2005) to 0.80 (in humans; Fay *et al*. 2001;
354 The Chimpanzee Sequencing and Analysis Consortium 2005). It follows that
355 nonsynonymous substitution rate may have a poor correlation with genetic load,
356 at least at larger taxonomic scales. However, the consensus proportion of
357 deleterious variants in Table 1 is between 0.05 and 0.25, which spans a smaller
358 range. Finally, dN/dS may in itself be a flawed estimate of functional divergence
359 because it relies on the assumptions that dS is neutral and mean dS can control
360 for substitution rate variation, which may not hold true, especially for closely
361 related taxa (Wolf *et al*. 2009; see also Kryazhimskiy and Plotkin 2008).
362
363 *Deleterious variants*
364 An increase in genetic load can come from: (1) increased frequency of
365 deleterious variants, (2) increased number of deleterious variants, and (3)
366 enrichment of deleterious variants relative to total variants. The first can be
367 assessed by examining shared deleterious variants between wild and
368 domesticated lineages, and all three by comparing both shared and private
369 deleterious variants across lineages. Looking at deleterious variants in high
370 frequency across all domesticated varieties may provide insight into the early
371 processes of domestication, while looking at deleterious variants with varying
372 frequencies among domesticated varieties may provide insight into the
373 processes of improvement. We recommend that researchers studying
374 deleterious variants present their results per genome, and then compare across
375 genomes and among lineages. Many, but not all, of the studies in Table 1 take
376 this approach. The total number, frequency, or proportion of deleterious variants
377 within a population will necessarily depend on the size of that population, and so
378 sufficient sampling is important before values can be compared across
379 populations. Values per genome are therefore easier to compare across most
380 available genomic datasets.

Renaut and Rieseberg (2015) found a significant increase in both shared and private deleterious mutations in domesticated relative to wild lines of sunflower, and similar patterns in two additional closely-related species: cardoon and globe artichoke (Table 1). This pattern also holds true for *japonica* and *indica* domesticated rice (Liu *et al*. 2017) and for the domesticated dog (Marsden *et al*. 2016) compared to their wild relatives (Table 1). In horses, deleterious mutation load as estimated using Genomic Evolutionary Rate Profiling (GERP) appears to be higher in both domesticated genomes and the extant wild relative (Przewalski's horse, which went through a severe genetic bottleneck in the last century) compared to an ancient wild horse genome (Schubert *et al*. 2014). These four studies, spanning a wide taxonomic range, suggest that an increase in the number and proportion of deleterious variants may be a general consequence of domestication. However, the other studies we present that examined deleterious variants in domesticated species did not include any sampling of wild lineages. Without sufficient sampling of a parallel lineage that did not undergo the process of domestication, it is difficult to assess whether the 'cost of domestication' is indeed general.

Identifying dangerous hitchhikers

The effect size of a deleterious mutation is negatively correlated with its likelihood of increasing in frequency through any of the mechanisms we discuss here. That is, variants with a strongly deleterious effect are more likely to be purged by selection than mildly deleterious variants, regardless of the efficacy of selection. Similarly, mutations that have a consistent, environmentally-independent deleterious effect are more likely to be purged than mutations with environmentally-plastic effects. In the extreme case, we would never expect mutations that have a consistently lethal effect in a heterozygous state to contribute to genetic load, as these would be lost in the first generation of their appearance in a population. However, mutations with consistent, highly deleterious effects are likely rare relative to those with smaller or environment-

412 dependent effects, especially in inbred populations (Figure 2A; Arunkumar *et al*.
413 2015). When thinking about genetic load, it is therefore important to recognize
414 that the effect of any particular mutation can depend on context, including
415 genomic background and developmental environment. This complexity likely
416 makes these classes of deleterious mutations more difficult to identify, and we
417 might not expect these variants to show up in our bioinformatic screens
418 (discussed below). Furthermore, all of these expectations are modified by
419 linkage: when deleterious variants are in LD with targets of artificial selection,
420 they are more likely to evade purging even with consistent, large, deleterious
421 effects (Figure 1B).
422
423 We searched the literature for examples of specific deleterious variants that
424 hitchhiked along with targets of selection during domestication and improvement.
425 We did not find many such cases, so we describe each in detail here. The best
426 characterized example comes from rice, where an allele that negatively affects
427 yield under drought (*qDTY1.1*) is tightly linked to the major green revolution
428 dwarfing allele *sd1* (Vikram *et al*. 2015). Vikram *et al*. (2015) found that the
429 *qDTY1.1* allele explained up to 31% of the variance in yield under drought across
430 three RIL populations and two growing seasons. Almost all modern elite rice
431 varieties carry the *sd1* allele (which increases plant investment in grain yield),
432 and as a consequence are drought sensitive. The discovery of the *qDTY1.1*
433 allele has enabled rice breeders to finally break the linkage and create drought
434 tolerant, dwarfed lines.
435
436 In sunflower, the *B* locus affects branching and was a likely target of selection
437 during domestication (Bachlava *et al*. 2010). This locus has pleiotropic effects on
438 plant and seed morphology that, in branched male restorer lines, mask the effect
439 of linked loci with both ‘positive’ (increased seed weight) and ‘negative’ (reduced
440 seed oil content) effects (Bachlava *et al*. 2010). To properly understand these
441 effects required a complex experimental design, where these linked loci were
442 segregated in unbranched (*b*) and branched (*B*) backgrounds. Managing these

443 effects in the heterotic sunflower breeding groups has likely also been
444 challenging.
445
446 A similarly complex narrative has emerged in maize. The gene *TGA1* was key to
447 evolution of 'naked kernels' in domesticated maize from the encased kernels of
448 teosinte (Wang *et al*. 2015). This locus has pleiotropic effects on kernel features
449 and plant architecture, and is in linkage disequilibrium with the gene *SU1*, which
450 encodes a starch debranching enzyme (Brandenburg *et al*. 2017). *SU1* was
451 targeted by artificial selection during domestication (Whitt *et al*. 2002), but also
452 appears to be under divergent selection between Northern Flints and Corn Belt
453 Dents, two maize populations (Brandenburg *et al*. 2017). This is likely because
454 breeders of these groups are targeting different starch qualities, and this work
455 may have been made more difficult by the genetic linkage of *SU1* with *TGA1*.
456
457 In the above cases, the linked allele(s) with negative agronomic effects are
458 unlikely to be picked up in a genome-wide screen for deleterious variation, as
459 they are segregating in wild or landrace populations and are not necessarily
460 disadvantageous in other contexts. One putative 'truly' deleterious case is in
461 domesticated chickens, where a missense mutation in the thyroid stimulating
462 hormone receptor (*TSHR*) locus sits within a shared selective sweep haplotype
463 (Rubin *et al*. 2010). However, Rubin *et al*. (2010) argue this is more likely a case
464 where a 'deleterious' (i.e. non-conserved) allele was actually the target of artificial
465 selection and potentially contributed to the loss of seasonal reproduction in
466 chickens.
467
468 In the Roundup Ready (event 40-3-2) soybean varieties released in 1996, tight
469 linkage between the transgene insertion event and another allele (or possibly an
470 allele created by the insertion event itself) reduced yield by 5-10% (Elmore *et al*.
471 2001). This is not quite genetic hitchhiking in the traditional sense, but the yield
472 drag effect persisted through backcrossing of the transgene into hundreds of
473 varieties (Benbrook 1999). This effect likely explains, at least in part, why

474 transgenic soybean has failed to increase realized yields (Xu *et al*. 2013). A
475 second, independent insertion event in Roundup Ready 2 Yield® does not suffer
476 from the same yield drag effect (Horak *et al*. 2015).
477
478 It is likely that 'dangerous hitchhiker' examples exist that have either gone
479 undetected by previous studies (possibly due to low genomic resolution, limited
480 phenotyping, or limited screening environments), have been detected but not
481 publicized, or are buried among other results in, for example, large QTL studies.
482 It is also possible that the role of genetic hitchhiking has not been as important in
483 shaping genome-wide patterns of genetic load as previously assumed.
484
485 <u>Gaps and Opportunities</u>
486 *For major improvement alleles, how much of the genome is in LD?*
487 Artificial selection during domestication targets a clear change in the optimal
488 multivariate phenotype. This likely affects a significant portions of the genome:
489 available estimates include 2–4% of genes in maize (Wright *et al*. 2005) and 16%
490 of the genome in common bean (Papa *et al*. 2007) targeted by selection during
491 domestication. For crops, traits such as seed dormancy, branching,
492 indeterminate flowering, stress tolerance, and shattering are known to be
493 selected for different optima under artificial versus natural selection (Takeda and
494 Matsuoka 2008; Gross and Olsen 2010). In some cases, we know the loci that
495 underlie these domestication traits. One well studied example is the green
496 revolution dwarfing gene, *sd1* in rice. *sd1* is surrounded by a 500kb region (~13
497 genes) with reduced allelic diversity in *japonica* rice (Asano *et al*. 2011). Another
498 example in rice is the *waxy* locus, where a 250 kb tract shows reduced diversity
499 consistent with a selective sweep in temperate *japonica* glutinous varieties
500 (Olsen *et al*. 2006). The difference in the size of the region affected by these two
501 selective sweeps may be because the strength of selection on these two traits
502 varied, with weaker selection at *waxy* then *sd1*. Unfortunately, the relative
503 strength of selection on domestication traits is largely unknown, and other factors
504 can also influence the size of the genomic region affected by artificial selection.

505 The physical position of selected mutation can have large effect on this via gene
506 density and local recombination rate (e.g. in rice, Flowers *et al*. 2012). This
507 explanation has been invoked in maize (Wright *et al*. 2005), where the extent of
508 LD surrounding domestication loci is highly variable. For example a 1.1 Mb
509 region (~15 genes) lost diversity during a selective sweep on chromosome 10 in
510 maize (Tian, Stevens, and Buckler 2009), but only a 60–90 kb extended
511 haplotype came with the *tb1* domestication allele (Clark *et al*. 2004). While these
512 case studies provide examples of sweeps resulting from domestication, they also
513 show that the size of the affected region is highly variable, and we don't yet know
514 how this might impact genetic load. This is compounded by the fact that even in
515 highly researched species we don't always know what were the genomic targets
516 of selection during domestication (e.g., in maize; Hufford *et al*. 2012), especially if
517 any extended LD driven by artificial selection has eroded or the intensity or mode
518 of artificial selection has changed over time.
519
520 *What's "worse" in domesticated species: hitchhikers, drifters, or inbreds?*
521 We do not have a clear sense of which evolutionary processes contribute most to
522 genetic load, and sometimes see contrasting patterns across species. In maize,
523 relatively few putatively deleterious alleles are shared across all domesticated
524 lines (hundreds vs. thousands; Mezmouk and Ross-Ibarra 2014), which points to
525 a larger role for the process of improvement than for domestication in driving
526 genetic load. In contrast, the increase in dog dN/dS relative to wolf populations
527 appears to not be driven by recent inbreeding (i.e., improvement) but by the
528 ancient domestication bottleneck common to all dogs (Marsden *et al*. 2016).
529
530 Of the deleterious alleles segregating in more than 80% of maize lines, only 9.4%
531 show any signal of positive selection (Mezmouk and Ross-Ibarra 2014). This
532 suggests that hitchhiking during domestication played a relatively small role in
533 the evolution of deleterious variation in maize. The same study found little
534 support for enrichment of deleterious SNPs in areas of reduced recombination
535 (Mezmouk and Ross-Ibarra 2014). However, Rodgers-Melnick *et al*. (2015)

536 present contrasting evidence supporting enrichment of deleterious variants in
537 regions of low recombination, and the authors argue that this difference is due to
538 the use of a tool that does not rely on genome annotation (Genomic Evolutionary
539 Rate Profiling, or GERP; Cooper *et al*. 2005). This complex narrative has
540 emerged from just one domesticated system, and it is likely that each species will
541 present new and different complexities.
542
543 *Specific differences*
544 Examining general differences between wild and domesticated lineages ignores
545 species-specific demographic histories and changes in life history, which may be
546 important contributors to genetic load. Although we found some general patterns
547 (e.g., loss of genetic diversity, Table 1), we also see clear exceptions (e.g., the
548 Andean common bean). We can attribute these exceptions to particular
549 demographic scenarios (e.g., gene flow with Mesoamerican common bean
550 populations), assuming we have sufficient archeological, historical, or genetic
551 data. One clear problem is our inability to sample ancestral (pre-domestication)
552 lineages, and our subsequent reliance on sampling of current wild relative
553 lineages that have their own unique evolutionary trajectories. Sequencing ancient
554 DNA can provide some insight into the history of these lineages and their
555 ancestral states (e.g., in horses; Schubert *et al*. 2014). Currently, we know very
556 little about most domesticated species' histories. We are still working towards
557 understanding dynamics since domestication: even in highly-researched species
558 like rice, the number of domestication events and subsequent demographic
559 dynamics are hotly contested (Kovach, Sweeney, and McCouch 2007; Gross and
560 Zhao 2014; Chen, Huang, and Han 2016; Choi *et al*. 2017).
561
562 A second challenge, briefly mentioned above, is understanding the relative
563 importance of each of the factors in any particular domestication event. For
564 example, in rice the shift to selfing from outcrossing during domestication
565 appears to have played a larger role than the domestication bottleneck in
566 shaping genetic load (Liu *et al*. 2017). This is useful in understanding rice

567 domestication and its impact, but similar studies would need to be conducted
568 across domesticated species to understand the generality of this dynamic. It is
569 possible that general patterns may be drawn from subsets of domesticated
570 species (e.g., vertebrates versus vascular plants, short-lived versus long-lived,
571 outcrossing versus selfing versus clonally propagated etc.). For example, there
572 may be general differences between annual and perennial crops, including less
573 severe domestication bottlenecks and higher levels of gene flow from wild
574 populations in perennials (Miller and Gross 2011; Gaut, Díez, and Morrell 2015).
575
576 *Predictive algorithms*
577 The identification of individual deleterious variants typically relies on sequence
578 conservation. That is, if a particular nucleotide site or encoded amino acid is
579 invariant across a phylogenetic comparison of related species, a variant is
580 considered more likely to be deleterious. More advanced approaches use
581 estimates of synonymous substitution rates at a locus to improve estimates of
582 constraint on a nucleotide site (Chun and Fay 2009). The majority of 'SNP
583 annotation' approaches are intended for the annotation of amino acid changing
584 variants, although at least one (GERP++; Davydov *et al*. 2010) can be applied to
585 noncoding sequences in cases where nucleotide sequences can be aligned
586 across species. This estimation of phylogenetic constraint is heavily dependent
587 on the sequence alignment used, and so new annotation approaches have
588 sought to use more consistent sets of alignments across loci. Both GERP++ and
589 MAPP permit users to provide alignments for SNP annotation (Davydov *et al*.
590 2010; Stone and Sidow 2005). The recently reported tool BAD_Mutations (Kono
591 *et al*. 2016; Kono *et al*. bioRxiv) permits the use of a consistent set of alignments
592 for the annotation of deleterious variants by automating the download and
593 alignment of the coding portion of plant genomes from Phytozome and Ensembl
594 Plants, which include 50+ sequenced angiosperm genomes (Goodstein *et al*.
595 2010; Kersey *et al*. 2016). Currently, the tool is configured for use with
596 angiosperms, but could be applied to other organisms.
597

598 Using phylogenetic conservation may be problematic in domesticated species, as
599 relaxed, balancing, or diversifying selection in agricultural environments could lift
600 constraint on sites under purifying or stabilizing selection in wild environments
601 (assuming some commonalities within these environment types). In one such
602 case, two AGPase small subunit paralogs in maize appear to be under
603 diversifying and balancing selection, respectively, even though these subunits
604 are likely under selective constraint across flowering plants (Georgelis, Shaw,
605 and Hannah 2009; Corbi *et al*. 2010). Similarly, broadly 'deleterious' traits may
606 have been under positive artificial selection in domesticated species. The loci
607 underlying these traits could flag as deleterious in bioinformatic screens despite
608 increasing fitness in the domesticated environment. For example, the *fgf4*
609 retrogene insertion that causes chrondrodysplasia (short-leggedness) in dogs
610 would likely have a strongly deleterious effect in wolves, but has been positively
611 selected in some breeds of dog (Parker *et al*. 2009). Finally, bioinformatic
612 approaches that rely on phylogenetic conservation are likely to miss variants with
613 effects that are only deleterious in specific environmental or genomic contexts
614 (plastic or epistatic effects), or which reduce fitness specifically in agronomic or
615 breeding contexts. Specific knowledge of the phenotypic effects of putatively
616 deleterious mutations is necessary to address these issues, but as we discuss
617 below these data are challenging to obtain.
618
619 Information from the site frequency spectrum, or the number of times individual
620 variants are observed in a sample, can provide additional information about
621 which variants are most likely to be deleterious. In resequencing data from many
622 species, nonsynonymous variants typically occur at lower average frequencies
623 than synonymous variants (cf. Nordborg *et al*. 2005; Ross-Ibarra *et al*. 2009;
624 Günther and Schmid 2010). Mutations that annotate as deleterious are
625 particularly likely to occur at lower frequencies than other classes of variants
626 (Marth *et al*. 2011; Kono *et al*. 2016; Liu *et al*. 2017) and may be less likely to be
627 shared among populations (Marth *et al*. 2011).
628

629 Tools for the annotation of potentially deleterious variants continue to be
630 developed rapidly (see Grimm *et al*. 2015 for a recent comparison). This includes
631 many tools that attempt to make use of information beyond sequence
632 conservation, including potential effects of variant on protein structure or function
633 (Adzhubei *et al*. 2010) or a diversity of genomic information intended to improve
634 prediction of pathogenicity in humans (Kircher *et al*. 2014). This contributes to the
635 issue that the majority of SNP annotation tools are designed to work on human
636 data and may not be applicable to other organisms (Kono *et al*. *bioRxiv*). There is
637 the potential for circularity when an annotation tool is trained on the basis of
638 pathogenic variants in humans and then evaluated on the basis of a potentially
639 overlapping set of variants (Grimm *et al*. 2015). Even given these limitations,
640 validation outside of humans is more challenging because of a paucity of
641 phenotype-changing variants. To address this issue, Kono et al. (*bioRxiv*) report
642 a comparison of seven annotation tools applied to a set of 2,910 phenotype
643 changing variants in the model plant species *Arabidopsis thaliana*. The authors
644 find that all seven tools more accurately identify phenotyping changing variants
645 likely to be deleterious in *Arabidopsis* than in humans, potentially because the
646 larger N_e in *Arabidopsis* relative to human populations may allow more effective
647 purifying selection.
648
649 *No one is perfect, not even the reference*
650 Bioinformatic approaches can suffer from reference bias (Simons *et al*. 2014;
651 Kono *et al*. 2016). One particular challenge in the identification of deleterious
652 variants is that with reference-based read mapping, variants are typically
653 identified as differences from reference, then passed through a series of filters to
654 identify putatively deleterious changes. For example, most annotation
655 approaches single out nonsynonymous differences from references. Because a
656 reference genome, particularly when based on an inbred, has no differences
657 from itself, the reference has no nonsynonymous variants to annotate and thus
658 appears free of deleterious variants. A more concerning type of reference bias is
659 that individuals that are genetically more similar to the reference genome will

660 have fewer differences from reference and thus fewer variants that annotate as
661 deleterious. This pattern is observed by Mezmouk and Ross-Ibarra (2014), who
662 find fewer deleterious variants in the stiff-stalk population of maize (to which the
663 reference genome B73 belongs) than in other elite maize populations. Along
664 similar lines, because gene models are derived from the reference genome,
665 more closely related lines with more similar coding portions of genes will appear
666 to have fewer disruptions of coding sequence. Finally reference bias can
667 contribute to under-calling of deleterious variants, either when different alleles fail
668 to properly align to the reference or if the reference is included in a phylogenetic
669 comparison. Variants that are detected as a difference from reference may then
670 be compared against the reference in an alignment testing for conservation at a
671 site. This conflates diversity within a species with the phylogenetic divergence
672 that is being tested in the alignment. In cases where the reference genome
673 contains the novel (or derived) variant relative to the state in related species, the
674 presence of the reference variant in the alignment will cause the site to appear
675 less constrained. This last problem is easily resolved by leaving the species
676 being tested out of the phylogenetic alignment used to annotate deleterious
677 variants.
678
679 *Effect size*
680 The evidence we present supports the cost of domestication hypothesis, namely
681 that domesticated lineages carry heavier genetic loads than their wild relatives
682 (Table 1). However, the distribution of fitness effects of variants is important with
683 the regard to the total load within an individual or population (Henn *et al*. 2015).
684 In other words, it is the cumulative effect of the variants carried by an individual
685 that make up its genetic load, not simply what proportion of those variants is
686 'deleterious'. As we describe above, current bioinformatic approaches that rely
687 on phylogenetic conservation may identify a number of false positives (driven by
688 new fitness optima under artificial selection) or false negatives (with specific
689 epistatic, dominance, or environmentally-dependent effects). Functional and
690 quantitative genetics approaches provide means of assessing the phenotypic

691 effect of genetic variants, but there are practical limitations that limit the quantity
692 of evaluations that can be conducted.
693
694 One potential issue is that the phenotypic effect of a genetic variant often
695 depends on genomic background, through both dominance (interaction between
696 alleles at the same locus) and epistasis (interaction among alleles at different
697 loci). Evaluating the effect of these variants is consequently a complex task,
698 requiring the creation and evaluation of multiple classes of recombinant
699 genomes. Similarly, the environment is an important consideration in thinking
700 about effect size. As we saw with the yield under drought *qDTY1.1* allele in rice
701 (*Identifying dangerous hitchhikers*, above; Vikram *et al*. 2015), the effect of a
702 genetic variant can depend on developmental or assessment environment.
703 These kinds of variants might be expected to be involved in local adaptation in
704 wild populations (e.g., Monroe *et al*. 2016), and so would not show up in a screen
705 based on phylogenetic conservation. Nevertheless, these variants may be
706 important in breeding programs that target general-purpose genotypes with, for
707 example, high mean and low variance yields. Identifying these alleles requires
708 assessment in the appropriate environment(s) and large assessment populations
709 (as the power for detecting genotype-phenotype correlations generally scales
710 with the number of genotypes assessed). Addressing effect size in the
711 appropriate context(s) therefore involves challenges of scale. Fortunately, new
712 types of mapping populations (e.g., MAGIC) and high-throughput phenotyping
713 platforms that can enable this work are increasingly available across
714 domesticated systems. Given these tools and the resultant data, we should soon
715 be able to parameterize genomic selection and similar models with putatively
716 deleterious variants and test their cumulative effects.
717
718 *Heterosis*
719 In systems with hybrid production, complementation of deleterious variants
720 between heterotic breeding pools may contribute substantially to heterosis (e.g.,
721 in maize; Hufford *et al*. 2012; Mezmouk and Ross-Ibarra 2014; Yang *et al*.

722 bioRxiv). If this is broadly true, hybrid production may be an interesting solution
723 to the cost of domestication, as long as deleterious variants are segregating
724 rather than fixed in domesticated species. Theory suggests that the deleterious
725 variants that contribute to heterosis between populations with low levels of gene
726 flow are likely to be of intermediate effect, and may not play a large role in
727 inbreeding depression (Whitlock, Ingvarsson, and Hatfield 2000). Since fitness in
728 these contexts is evaluated in hybrid individuals rather than inbred parents,
729 parental populations are likely to retain a higher proportion of slightly and
730 moderately deleterious variants than even selfing populations (Figure 2A). As
731 long as hybrid crosses are the primary mode of seed production, these alleles
732 may not be of high importance to breeders even though they contribute to
733 genetic load more broadly. Evaluating effect size in this context requires
734 assessing both parental and hybrid populations, and is therefore that much more
735 difficult. However, assuming that complementation of deleterious variants is a
736 substantial component of heterosis, quantifying these variants should improve
737 the ability of breeding programs to predict trait values in hybrid crosses. Further,
738 the question of whether genetic load limits genetic gains in hybrid production
739 systems remains open.
740
741 CONCLUSIONS
742 Research on the putative costs of domestication is still relatively new, and there
743 remain many open questions. However, our review of the literature suggests that
744 genetic loads are generally heavier in domesticated species compared to their
745 wild relatives. This pattern is likely driven by a number of processes that
746 collectively act to reduce the efficacy of selection relative to drift in domesticated
747 populations, resulting in increased frequency of deleterious variants linked to
748 selected loci and greater accumulation of deleterious variants genome-wide. We
749 encourage further research across domesticated species on these processes,
750 and recommend that researchers: (1) Sample domesticated and wild lineages
751 sufficiently to assess diversity within as well as between these groups and (2)
752 present deleterious variant data per genome and as proportional as well as

absolute values. We also strongly encourage researchers and breeders to think about deleterious variation in context, both genomic and environmental.

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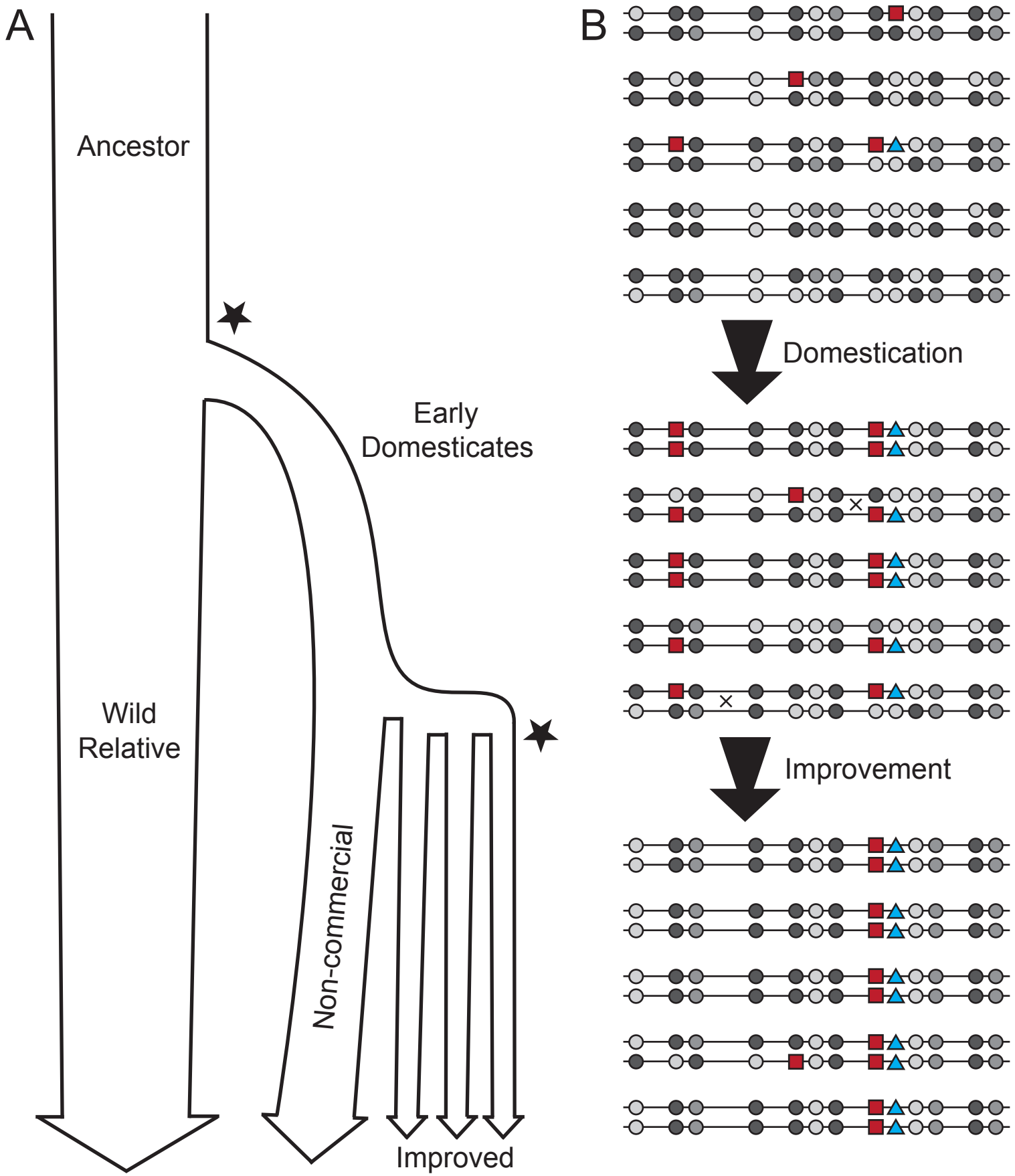
TABLES AND FIGURES

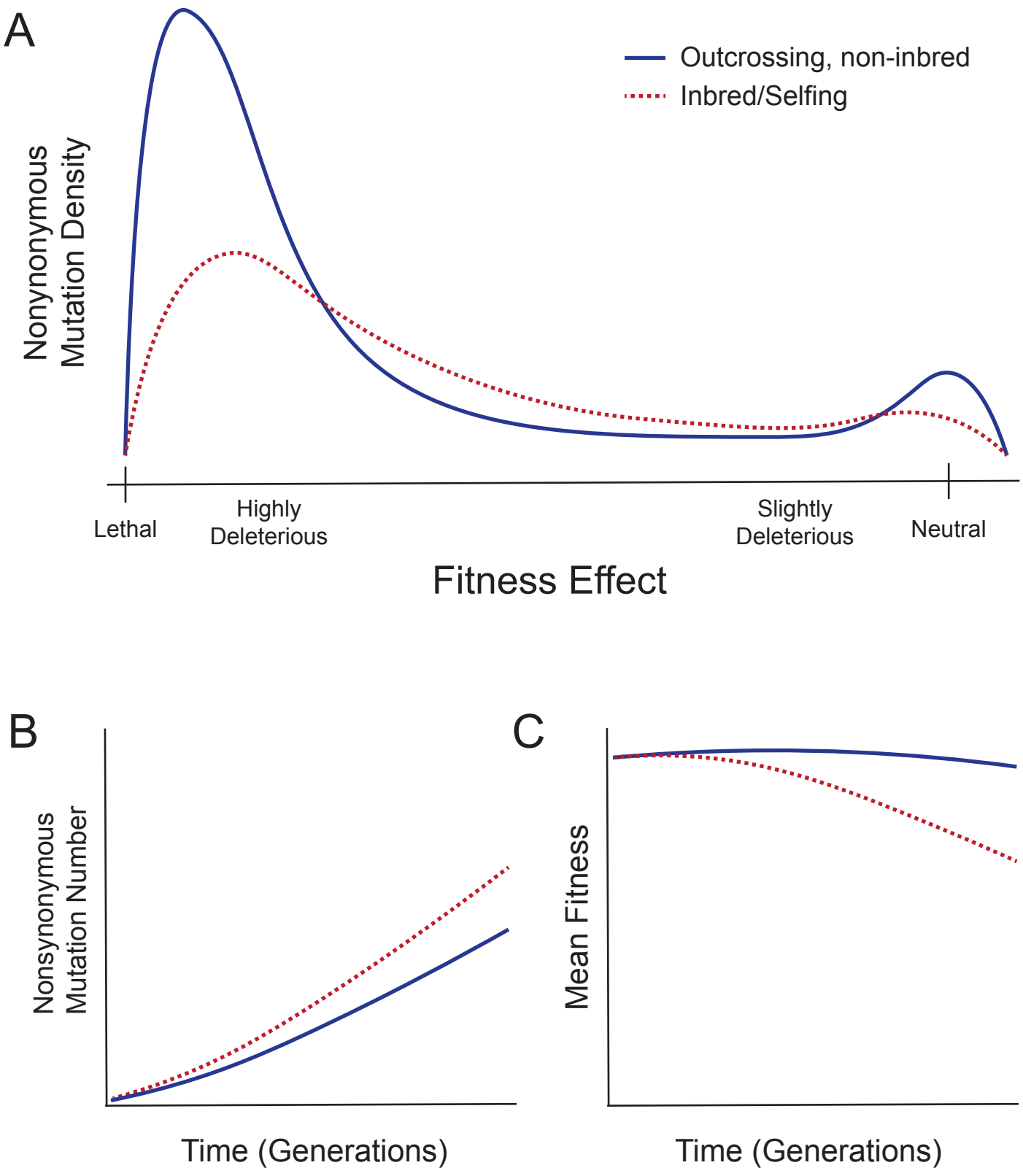
Table 1. Evidence for genetic load across domesticated plants and animals. *Arabidopsis thaliana* and *Homo sapiens* included for comparison. Plant 1C genome sizes from the RBG Kew database (http://data.kew.org/cvalues/), except tomato (Michaelson *et al*. 1991) and *Cynara* spp. (Giorgi *et al*. 2016). Plant chromosome counts from the Chromosome Counts Database (http://ccdb.tau.ac.il/). Animal 1C genome sizes and chromosome counts from the Animal Genome Size Database (http://www.genomesize.com/, mean value when multiple records were available). Gene numbers are high-confidence (if available) estimates from the vertebrate and plant Ensembl databases (http://uswest.ensembl.org/; http://plants.ensembl.org/), except common bean (Schmutz et al. 2013), sunflower (Compositate Genome Project, unpublished), and *Cynara* spp. (Scaglione et al. 2016). LD N50 is the approximate distance over which LD decays to half of maximum value. Loss of genetic diversity is calculated as 1 – (ratio of $p_{domesticated}$ to p_{wild}), or q if p not available.

Figure 1. Processes of domestication and improvement. (A) Typical changes in effective population size through domestication and improvement. Stars indicate genetic bottlenecks. These dynamics can be reconstructed by examining patterns of genetic diversity in contemporary wild relative, domesticated non-commercial, and improved populations. (B) Effects of artificial selection (targeting the blue triangle variant) and linkage disequilibrium on deleterious (red squares) and neutral variants (grey circles, shades represent different alleles). In the ancestral wild population, four deleterious alleles are at relatively low frequency (mean = 0.10) and heterozygosity is high (H_O = 0.51). After domestication, the selected blue triangle and linked variants increase in frequency (three remaining deleterious alleles, mean frequency = 0.46), heterozygosity decreases (H_O = 0.35), and allelic diversity is lost at two sites. Recombination may change haplotypes, especially at sites less closely linked to the selected allele (Xs). After improvement, further selection for the blue triangle allele has: lowered heterozygosity (H_O = 0.08), increased deleterious variant frequency (two remaining deleterious alleles, mean = 0.55), and lost allelic diversity at six additional sites.

Figure 2. Effects of inbreeding on mutations and fitness. (A) Theoretical density plot of fitness effects for segregating variants. In outcrossing, non-inbred populations (solid navy line), more variants with highly deleterious, recessive effects persist that are rapidly exposed to selection and purged in inbred populations (dotted red line), shifting the left side of the distribution towards more neutral effects. At the same time, the reduced effective population size created through inbreeding causes on average higher loss of slightly advantageous mutations and retention of slightly deleterious mutations, shifting the right side of

1302 the distribution towards more deleterious effects. (B) Accumulation of
1303 nonsynonymous mutations is accelerated in selfing individuals (dotted red line)
1304 relative to outcrossing individuals (solid navy line). Synonymous mutations
1305 accumulate at similar rates in both populations. Adapted from simulation results
1306 in Arunkumar *et al*. 2015. (C) As a consequence of (B), mean individual fitness
1307 drops in selfing relative to outcrossing populations. Adapted from Arunkumar *et*
1308 *al*. 2015.


A
Ancestor
Early
Domesticates
Wild
Relative
Non-commercial
Improved
B
Domestication
Improvement


A
Outcrossing, non-inbred
Inbred/Selfing
Nonynonymous Mutation Density
Lethal
Highly Deleterious
Slightly Deleterious
Neutral
Fitness Effect
B
Nonsynonymous Mutation Number
Time (Generations)
C
Mean Fitness
Time (Generations)

Species	Primary reproduction	Genome size (1C, pg)	Chromosome number (N)	Protein coding genes	Non-coding genes	LD N50	LD N50 in wild	Loss of genetic diversity	dN/dS domesticated to dN/dS wild (or Ka/Ks)*	GERP score load increase relative to wild	Genome-wide deleterious variant number	Deleterious variant proportion (of nonsynonymous variants)	Deleterious variants in wild, # (proportion)	Method(s) for deleterious variant detection	Studies
japonica rice (Oryza sativa var japonica)	selfing	0.50	12	35,679	55,401	167 kb	20 kb	0.67	1.70	NA	~6295*	0.19*	6099 (0.15)*	SIFT, PROVEAN	Lu et al. 2006; Huang et al. 2012; Liu et al. 2017
indica rice (Oryza sativa var indica)	selfing	0.50	12	40,745	45,577	123 kb	20 kb	0.25	1.75	NA	~6351*	0.18*	6099 (0.15)*	SIFT, PROVEAN	Lu et al. 2006; Huang et al. 2012; Liu et al. 2017
African rice (Oryza glaberrima)	selfing	0.83	12	33,164	38,882	~25 Mb*	NA	0.60	1.58	NA	NA	NA	NA		Semon et al. 2005; Nabholz et al. 2014
maize (Zea mays)	outcrossing	2.73	10	39,498	4,976	<1 kb	NA	0.17	NA	NA	~1025–4056*	0.04–0.16*	NA	SIFT, MAPP; Join of these	Gore et al. 2009; Hufford et al. 2012; Mezmouk and Ross-Ibarra 2014
barley (Hordeum vulgare)	selfing	5.55	7	24,287	1,512	~2.2 Mb	~110 kb	0.13 (domestication) and 0.27 (improvement)	2.43–4.60	NA	1,006–3,400	0.06–0.19	NA	SIFT, PolyPhen2, LRT, Intersect of these	The International Barley Genome Sequencing Consortium 2012; Morrell et al. 2014; Shi et al. 2015; Kono et al. 2016
soybean (Glycine max)	selfing	1.13	20	54,174	NA	83 kb (domesticated) and 123 kb (improved)	27 kb	0.52 (domestication) and 0.64 (improvement)	1.01**	NA	784–3,881	0.03–0.13	NA	SIFT, PolyPhen2, LRT, Intersect of these	Lam et al. 2010; Zhou et al. 2015; Kono et al. 2016
common bean (Phaseolus vulgaris, Mesoamerican domestication)	selfing	0.60	11	27,197	NA	NA	NA	0.20	NA	NA	NA	NA	NA		Schmutz et al. 2013
common bean (Phaseolus vulgaris, Andean domestication)	selfing	0.60	11	27,197	NA	NA	NA	-0.50	NA	NA	NA	NA	NA		Schmutz et al. 2013
tomato (Solanum lycopersicum)	selfing	1.00	12	33,837	4,849	257 kb (domesticated) and 866 kb (improved)	9 kb	0.46 (domestication) and 0.77 (improvement)	1.37***	NA	NA	NA	NA		Koenig et al. 2013; Lin et al. 2014
sunflower (Helianthus annuus)	outcrossing	2.43	17	52,232	NA	~1 kb	200 bp	0.33	NA	NA	5,626–20,273*	0.14–0.17*	7,882–24,479 (0.12–0.14)*	PROVEAN	Liu and Burke 2006; Mandel et al. 2011; Renaut and Rieseberg 2015; L. Rieseberg unpublished
globe artichoke (Cynara cardunculus var. scolymus)	clonal propogation, outcrossing	1.20	17	26,889	NA	NA	NA	NA	NA	NA	1,537–1,889*	0.19–0.20*	1,465 (0.17)*	PROVEAN	Renaut and Rieseberg 2015
cardoon (Cynara cardunculus var. altilis)	outcrossing	1.10	17	26,889	NA	NA	NA	NA	NA	NA	1,239–1,458*	0.22–0.23*	1,900 (0.19)*	PROVEAN	Renaut and Rieseberg 2015
thale cress (Arabidopsis thaliana)	*selfing*	*0.30*	*5*	*27,655*	*1,398*	*~3.4 kb*	*NA*	*NA*	*NA*	*NA*	*8,831–9,584*	*0.19–0.21*	*NA*	*SIFT, MAPP*	*Kim et al. 2007; Günther and Schmid 2010*
chicken (Gallus gallus domesticus)	outcrossing	1.25	39	18,346	6,492	~50–250 kb	< 50 kb	~0.50 (from domesticated to 'commercial' breeds*)	NA	NA	35,889–88,655	0.20–0.49	NA	SIFT, PROVEAN, Join and Intersect of these	Muir et al. 2008; Megens et al. 2009; Gheyas et al. 2015
dog (Canis familiaris)	outcrossing	3.12	39	19,856	11,898	~100 kb	< 10 kb	0.05 (domestication) / 0.35 (breed formation)	1.54	2.1%	~5,115*	~0.14	~4,990 (~0.138)*	Mivata distance; GERP	Lindblad-Tor *et al. 2005*; Cruz, Vila & Webster 2008; Gray et al. 2009; Marsden et al. 2016
horse (Equus caballus)	outcrossing	3.22	32	20,449	2,142	~200 kb	NA	0.40**	NA	1.1–11%	NA	NA	NA	GERP	Lau et al. 2009; Wade et al. 2009; Schubert et al. 2014
pig (Sus scrofa)	outcrossing	3.17	19	21,630	3,124	5 kb–1 Mb	< 50 kb	0.19	NA	NA	656*	NA	NA	SIFT	Amaral et al. 2008; Bosse et al. 2012; Bosse et al. 2015
human (Homo sapiens)	*outcrossing*	*3.50*	*23*	*20,441*	*22,219*	*22–44 kb*	*NA*	*NA*	*1.03*	*NA*	*796–838**	*0.08–0.15**	*NA*	*LRT*	*Gabriel et al. 2002; Chun and Fay 2009; Scally et al. 2012*
						* likely due to population structure in sampled accessions (Semon et al. 2005)		*estimated as portion of hypothetical ancestral allele frequency distribution lost	* or versus sister species for human		* per genome	* per genome	*significantly lower in wild		
								** autosomal nucleotide diversity only	** data are ratio of nonsynonymous to synonymous SNP counts rather than substitutions						
									*** comparison of domesticated lineage versus whole tree rates (five wild lineages and one domesticated)						