Population size may shape the accumulation of functional mutations following domestication

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Abstract

Background: Population genetics theory predicts an important role of differences in the effective population size (Ne) among species on shaping the accumulation of functional mutations by regulating the selection efficiency. However, this correlation has never been tested in domesticated animals.

Results: Here, we synthesized 62 whole genome data in eight domesticated species (cat, dog, pig, goat, sheep, chicken, cattle and horse) and compared domesticates with their wild (or ancient) relatives. Genes with significantly different selection pressures (revealed by nonsynonymous/synonymous substitution rate ratios, Ka/Ks or ω) between domesticated (Dω) and wild animals (Wω) were determined by likelihood-ratio tests. Species-level effective population sizes (Ne) were evaluated by the pairwise sequentially Markovian coalescent (PSMC) model, and Dω/Wω were calculated for each species to evaluate the changes in accumulation of functional mutations after domestication relative to pre-domestication period. Correlation analysis revealed that the most recent (~ 10,000 years ago) Ne(s) are positively correlated with Dω/Wω. This result is consistent with the corollary of the nearly neutral theory, that higher Ne could boost the efficiency of positive selection, which might facilitate the overall accumulation of functional mutations. In addition, we also evaluated the accumulation of radical and conservative mutations during the domestication transition as: Dradical/Wradical and Dconservative/Wconservative, respectively. Surprisingly, only Dradical/Wradical ratio exhibited a positive correlation with Ne (p < 0.05), suggesting that domestication process might magnify the accumulation of radical mutations in species with larger Ne.

Conclusions: Our results confirm the classical population genetics theory prediction and highlight the important role of species’ Ne in shaping the patterns of accumulation of functional mutations, especially radical mutations, in domesticated animals. The results aid our understanding of the mechanisms underlying the accumulation of functional mutations after domestication, which is critical for understanding the phenotypic diversification associated with this process.

Keywords: Purifying selection, Positive selection, Selection dynamics, Effective population size

Background

In one of his major works, The Variation of Animals and Plants Under Domestication, Darwin observed that domestication is the process during which striking phenotypic variation burgeons [1]. Much later, it has been suggested that the diversification of phenotypic variation in domesticated species might be attributed to the faster accumulation of functional (nonsynonymous) variants [2–4]. However, genome-wide patterns of accumulation of functional mutations pre- and post-domestication across different domesticated species are still poorly understood. According to the population genetics theory, fates of genetic variations may lie in the coupled effect of changes in selection intensities and effective population sizes (Ne) [5]. Against this backdrop of theoretical prediction, it is reasonable to evaluate the relative efficiency of
mutation accumulation before and after domestication in the context of both selection and Ne.

It has been theorized that selection may act upon domesticates in a stage-dependent manner [3, 6]. More specifically, domestication may begin with an unintentional process (unconscious selection), characterized by the relaxation of selection constraints vital in wild environments, alongside the introduction of novel selection forces [7]. These early shifts in selection constraints may have contributed to the emergence of domestication-facilitating traits, such as increased docility and tameness, which are thought to be prerequisites for the whole domestication process [8]. Although the early (unconscious) domestication began thousands of years ago, deliberate human selection is a process that emerged within the recent three centuries through intensive breeding, which has led to rapid improvement of desirable traits and creation of most modern breeds [9, 10].

In addition to selection, another critical factor influencing the accumulation of mutations is the changes in Ne. Unlike selection, the effect of population size on genome evolution is independent of specific domestication episodes. Once domestic populations formed and became isolated from their wild relatives, genetic drift, characterized by diminished Ne, came to influence the domestication processes [11]. In this sense, although the eye-catching feature of domestication is selection itself, it (selection) has to “dance with shackles on” as the end results of selection are largely shaped within the frame of lineage Ne.

Quantitatively, the magnitude of selection is commonly measured by the ratio of the number of nonsynonymous substitutions per nonsynonymous site (Ka) to the number of synonymous substitutions per synonymous site (Ks) - Ka/Ks (ω); where ω < 1 indicates purifying selection, ω = 1 - neutral selection, and ω > 1 - positive selection [12–14]. Variations in selection strength may tune the amount of mutations: studies have found that domesticated animals accumulate functional mutations in some mitochondrial genes much faster than their wild relatives, probably due to differences in Ne [14].

Historical effective population sizes across species
As accumulation of nonsynonymous mutations is influenced by Ne, especially at the species level [14], we inferred historical demography by the pairwise sequentially
Markovian coalescent (PSMC) model [23], using resequencing data of wild animals with the highest read depth (Additional file 1, Fig. 1). Parameters for the PSMC analysis were “-N25 -t15 -r5 -p "4 + 25*2 + 4 + 6"”.

Reference-mapping assembly and CDS extraction

Given that some of the species included in the analysis (cattle, dog, sheep, goat, cat, horse and chicken) have only one or two publicly available genome assemblies and gene annotations, a reference-mapping assembly approach was used to generate genome sequences of all downloaded short reads [24]. Sequencing adaptors removal and data quality control were performed using Trimmmomatic-0.35 and FastQC [25, 26]. Reads were discarded if Phred quality was < 20 over three consecutive base pairs (bp) and shorter than 40 bp. Reference-mapping was carried out with Bowtie2, with a very sensitive alignment setting following suggestions in the manual [27]. After sorting the aligned bam files by Samtools v1.1, other tools in this package, including mpileup, bcftools and vcfutils, were invoked to produce the target genomes [28, 29]. These target genomes were then used to extract the corresponding CDS sequences with gKaks v1.3 program by incorporating both CDS and gene annotation (gff or gtf) of public reference [30].

The dynamics of selective pressure

To calculate phylogeny-based Ka/Ks (ω) for each CDS in each individual of a species, we generated phylogenies and alignments as input files. Non-homologous sequences, multiple frame shift mutations and early stop codons were deleted by BLAT [31] and bl2seq [32]. In total, the number of sequence alignments varied from 14,441 in chicken to 23,019 in dog (Fig. 1). We produced the phylogeny-aware alignments by invoking the codon model in PRANK [33]. We randomly selected 1000 alignments of orthologs (determined using 1:1 orthologs from the BioMart database [34]) with at least 1 k bp to compute the maximum likelihood gene trees using RAxML [35], with 100 fast bootstrap replicates. Based on these gene trees, we used STAR [36] to infer phylogenetic trees for all studied species (Additional file 2).

Based on these alignments and phylogenetic trees, we calculated Ka/Ks ratios for two types of branches, “wild” and “domesticates”, using PAML [37]. To further determine the significance level between them, we used “likelihood ratio test” (LRT) to compare two models, “two-ratios model” (TRM) and “one-ratio model” (ORM), with the chi-square approximation. TRM hypothesis assumes a different ratio between domesticates and wild branches, whereas ORM assumes the same ω for all branches. For the Ka/Ks ratios with extreme values, where only nonsynonymous or only synonymous mutations were detected, we kept them only if they were statistically significant [14]. For both domesticated and wild/ancient branches, the mean ω values of significantly different genes (Table 1, Fig. 2) were measured. In addition, accumulation levels of functional mutations at post-domestication stages relative to pre-domestication stages were compared using a novel metric: \(D_ω/W_ω\), where D is a domesticated group and W a wild group (Fig. 3a). Since annotation artefacts of reference genomes equally affect domesticated and wild groups, this metric has the advantage of avoiding biases caused by different annotations. Selection dynamics types (see Introduction) were identified based on all arithmetic possibilities of Ka/Ks changes (Table 2). By doing so, we can examine (a) whether the overall proportion of non-synonymous mutations has increased after domestication in different species; and (b) whether these changes might be due to specific type(s) of selection dynamics.

Conservative and radical functional changes

It has been suggested that a high frequency of nonsynonymous mutations can lead to an increased ratio of radical mutations [38]. Here we categorized and compared radical and conservative nonsynonymous mutations based on physiochemical properties of proteins, such as amino acid charge, polarity and volume [39]. Conservative mutations are the changes wherein proteins retain similar physiochemical properties, whereas radical mutations are the ones with radical changes in physiochemical features of proteins. We evaluated the occurrence of radical and conservative changes per lineage based on a previously proposed method [39]. Subsequently, the changes after domestication relative to before domestication were calculated by two metrics: \(D_{\text{conservative}}/W_{\text{conservative}}\) and \(D_{\text{radical}}/W_{\text{radical}}\) (Fig. 3a). Significance tests were performed using G-test (Fig. 4), and Pearson correlation analysis was conducted to evaluate whether the patterns of \(D_ω/W_ω\), \(D_{\text{conservative}}/W_{\text{conservative}}\) and \(D_{\text{radical}}/W_{\text{radical}}\) changed between domesticates and wilds.

Table 1

| Species | No. of genomes | Total transcripts | Differential transcripts | \(D_ω\) | \(W_ω\) |
|---------|----------------|------------------|-------------------------|-------|-------|
| Cat     | 6              | 19,991           | 221                     | 556.51| 115.42|
| Dog     | 8              | 16,685           | 183                     | 184.66| 87.49 |
| Pig     | 15             | 18,660           | 556                     | 347.57| 70.62 |
| Chicken | 8              | 14,441           | 84                      | 230.2 | 230.17|
| Goat    | 4              | 16,680           | 342                     | 316.76| 168.65|
| Sheep   | 8              | 19,860           | 157                     | 243.32| 146.8 |
| Cattle  | 6              | 19,881           | 179                     | 185.16| 200.47|
| Horse   | 7              | 18,954           | 205                     | 95.38 | 280.92|

Number of genomes analyzed per species, all transcripts used, transcripts with statistically significant differences, and genome-wide Ka/Ks ratios in domesticates ("D") and their wild relatives ("W")

| Species | No. of genomes | Total transcripts | Differential transcripts | \(D_ω\) | \(W_ω\) |
|---------|----------------|------------------|-------------------------|-------|-------|
| Horse   | 7              | 18,954           | 205                     | 95.38 | 280.92|

Table 1 Genomes of the eight studied species

Number of genomes analyzed per species, all transcripts used, transcripts with statistically significant differences, and genome-wide Ka/Ks ratios in domesticates ("D") and their wild relatives ("W")
$W_{\text{conservative}}$ and $D_{\text{radical}}/W_{\text{radical}}$ across different species might be correlated with $N_e$ (Fig. 3b, c, d).

**Results and discussion**

Previous studies have observed faster accumulation of non-silent mutations following domestication in some animals, including dog, pig, yak and chicken, which is believed to be a consequence of a decrease in $N_e$ associated with domestication and relaxation of purifying selection on mitochondrial genes in some domesticated species [2, 16, 17], but the debate on whether all domesticated animals exhibit a consistent trend is still ongoing [40]. Considering large $N_e$ differences across species, it would be very interesting to investigate whether the
accumulation of functional mutations post- and pre-domestication might exhibit interspecific heterogeneities.

Although more than 14,441 transcripts were analyzed for each species, LRT detected less than 600 genes exhibiting significant ($p < 0.05$) differences between domesticates and their wild or ancient relatives (Table 1, Additional file 3). Intriguingly, two opposite patterns were observed among the significant $\omega$ for the eight species: dog, cat, pig, goat, sheep and chicken have higher $\omega$ in domesticates than in their corresponding wild relatives, whereas in horse and cattle this trend is reversed (Fig. 2 and Table 1). This pattern was further confirmed by $D_\omega/W_\omega$ ratio (Fig. 3a), which was used to avoid biases caused by putative differences in the level of annotation among species. These ratios are lower than 1 in cattle and horse but higher than 1 in the other six species. Interestingly, studies have revealed that, in comparison to small animals, large animals exhibit higher levels of slightly deleterious mutations, which may lead to population decline or even extinction [41]. In this study, the ancestors of the two largest animals, cattle and horse, exhibited the highest $\omega$ ratios among the wild

**Fig. 2** Beanplot of $Ka/Ks$ ratios for all differential genes between domesticates and corresponding wild relatives. Red lines represent overall mean values for wild species (W) and domesticates (D) of the eight species. Blue and violet curves are density traces of $Ka/Ks$ ratios for W and D, respectively. Cyan and green small lines are individual $Ka/Ks$ ratio for W and D, respectively.
relatives of the eight studied species, indicating that they had accumulated the highest amount of (slightly) deleterious mutations.

To evaluate the functional effects of nonsynonymous mutations, we categorized them as radical or conservative. We found that the numbers of radical mutations are universally higher than the numbers of conservative mutations in both domesticates and their progenitors for all eight species (Fig. 4). When we further compared D_{\text{conservative}}/W_{\text{conservative}} and D_{\text{radical}}/W_{\text{radical}} ratios across species, we observed that both of these metrics are lower than 1 for cattle and horse and higher than 1 for the remaining six species (Fig. 3a). Hence, these results suggest that domesticates may not share a common trend in terms of the accumulation of non-silent mutations.

Interestingly, it seems that the most parsimonious distinction between the two groups of species revealed from our results is the body-mass, as cattle and horse
have more than three times higher body-mass than any of the remaining six species (Fig. 3a). Thus, for the sake of convenience, we can term the two groups as “LD” (large body-mass domesticates, including cattle and horse) and “SD” (small body-mass domesticates, including cat, dog, pig, goat, sheep, and chicken). In the field of evolutionary genetics, body-mass (or generation time) has usually been used as a proxy for \(N_e\) due to the inverse relationship between them [42–47].

To analyze how different \(N_e\) may be involved in affecting the selection efficiency, we evaluated their \(N_e\)s using the PSMC method. Since this method can only infer historical demography on an ancient time-scale (~10,000 years ago) [23], it is appropriate for comparisons of long-term interspecies differences in \(N_e\). PSMC analysis revealed that LD species have lower most recent (~10,000 years ago) \(N_e\) than SD species (Fig. 1). This difference in \(N_e\) is roughly consistent with the predicted negative relationship between body-mass (or generation time) and \(N_e\) [42–47] (Fig. 3a).

Pearson correlation revealed that \(D_\omega/W_\omega\) is significantly correlated with \(N_e\)s in all eight species \((p < 0.05,\) Fig. 3b), which is consistent with theoretical population genetics expectations. Nearly neutral theory suggests that the effect of selection depends on the product of the effective population size \(N_e\) and selection coefficient \(s\) \((N_e s)\) [5, 48]. Later, the relationship between \(\omega, N_e\) and selection coefficient \((s)\) has been formulated as \(\omega = \frac{S}{1 + S}\), where \(S = 4N_e s\) [49]. According to the formula, to achieve the same changes in \(\omega\), species with smaller \(N_e\) would have to undergo much bigger changes in selection coefficient. In other words, selection is expected to be inefficient in species with small \(N_e\), either when it comes to accumulation of beneficial functional mutations (through positive selection), or to removal of deleterious functional mutations (by purifying selection). In contrast, selection efficiency would be higher in populations with higher \(N_e\) [50]. Thus, the main factor contributing to the lower Ka/Ks after domestication in LD species, observed in this study, might be their lower \(N_e\)s, which resulted in lesser efficiency of positive selection to accumulate beneficial mutations. We also observed a positive relationship between \(D_{\text{radical}}/W_{\text{radical}}\) and \(N_e\) (Fig. 3d), which suggests that higher \(N_e\) might also

| Species | More mutations | Less mutations | UN |
|---------|----------------|----------------|----|
|         | PST | IPS | RPR | RPS | IPR | PRI |
| Cat     | 155 | 0   | 36  | 1   | 3   | 26  | 0   |
| Dog     | 47  | 7   | 50  | 5   | 19  | 42  | 13  |
| Chicken | 32  | 2   | 11  | 0   | 11  | 20  | 8   |
| Goat    | 171 | 1   | 44  | 0   | 36  | 83  | 7   |
| Sheep   | 75  | 0   | 24  | 0   | 16  | 38  | 0   |
| Pig     | 290 | 3   | 116 | 2   | 70  | 64  | 11  |
| Horse   | 31  | 2   | 14  | 2   | 61  | 94  | 1   |
| Cattle  | 52  | 1   | 18  | 1   | 34  | 73  | 0   |

UN stands for the number of genes with unchanged selection pressure.

Table 2 The number of genes under different directions of selection dynamics

Fig. 4 Numbers of radical and conservative mutations in domesticates and corresponding extant or ancient wild relatives. Stars above the horse indicate a significant difference (G-test, \(p = 0.048\)) between radical and conservative mutations. Note: red and blue bars represent the numbers of conservative and radical mutations per lineage, respectively; to save space, they have been partially overlapped. “D” represents domesticated species and “W” represents wild species.
drive a faster accumulation of radical mutations, as a result of a more efficient positive selection. This conclusion was further confirmed by our selection dynamics analysis (Table 2), where we found that the SD species with higher $N_e$ have more genes under higher positive selection (PST + IPS). Thus, our results revealed that under the frame of higher $N_e$ the efficiency of positive selection may be promoted at the post-domestication stage.

Taken together, we detected a positive relationship between the interspecies variation in $N_e$ and the tempo of accumulation of functional mutations, indicating the existence of interspecific heterogeneity in the efficiency of selection. It is worth noting that, since our study was only limited to protein-coding regions, future efforts should be made to explore how the effects of regulatory elements might be influenced by population parameters, considering their important roles in domestication [51].

**Conclusions**

Animal domestication presents a unique opportunity to study how the joint effects of selection and drift influence the accumulation of mutations, especially on a genome-wide scale. Rapidly-increasing amount of available genomic data offers us an opportunity to explore whether the differences in interspecific demography might result in different rates of accumulation of functional mutations, as predicted by theoretical population genetics. In this study, we found that $D_{\omega}/W_{\omega}$ and $D_{\omega}/W_{\omega}$ are positively correlated with the species-level effective population sizes. Our results suggest that the impact of $N_e$ on the accumulation of functional (including radical) mutations might be underestimated, and emphasize the importance of maintaining a large population size for strengthening the efficiency of selection in animal breeding.

**Additional files**

**Additional file 1:** The data for 62 genomes from eight species. Data used in the study, including species, status (domestic or wild, where breed is indicated for domestic animals), accession ID with the corresponding reference, and read depth. (DOXC 44 kb)

**Additional file 2:** Figure S1. Phylogenetic trees for the eight species. Phylogenetic trees for the eight studied species. The red branches represent domesticated branches. The blue branches are background branches. (DOXC 388 kb)

**Additional file 3:** Statistically significant genes detected with LRT and their Ka/Ks ratios. Genes exhibiting significant differences between domesticates and their wild or ancient relatives detected by the likelihood ratio test (LRT). Information included: transcript ID, gene names, $p$ values of the LRT test, Ka/Ks values of wild lineages (W), and Ka/Ks of domesticated lineages (D). (DOXC 190 kb)

**Abbreviations**

$D_{\text{conservative}}/W_{\text{conservative}}$: The conservative changes after domestication relative to before domestication; $D_{\text{radical}}/W_{\text{radical}}$: The radical changes after domestication relative to before domestication; $D_{\omega}$: Ka/Ks of domesticated species or animals; $D_{\omega}/W_{\omega}$: Ka/Ks of domesticated species or animals relative to that of wild species or animals; IPR: Intensified purifying selection $(1 > W_{\omega} > D_{\omega})$; IPS: Intensified positive selection $(D_{\omega} > W_{\omega} > 1)$; Ka/Ks: The ratio of the number of nonsynonymous substitutions per nonsynonymous site ($K_a$) to the number of synonymous substitutions per synonymous site ($K_s$); LD: Large body-mass domesticates, including cattle and horse; LRT: Likelihood ratio test; $N_e$: Effective population sizes; ORM: One-ratio model; PRT: Purifying selection transition ($W_{\omega} < 1$; $D_{\omega} < 1$); PSMC: Pairwise sequentially Markovian coalescent; PST: Positive selection transition ($W_{\omega} < 1$; $D_{\omega} > 1$); RPR: Relaxed purifying selection $(1 > D_{\omega} > W_{\omega})$; RIP: Relaxed positive selection ($W_{\omega} > D_{\omega} > 1$); $s$: Selection coefficient; SD: Small body-mass domesticates, including cat, dog, pig, goat, sheep, and chicken; TRM: Two-ratios model; $W_{\omega}$: Ka/Ks of wild species or animals

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**Availability of data and materials**

The datasets supporting the conclusions of this article are included within the article and its Additional files.

**Authors’ contributions**

JHC and SHZ initiated and conceived the project. JHC, PN, XYL, JLH, and CJZ performed the analyses. JHC wrote the manuscript. IJ and CJZ critically revised and edited the manuscript. All authors contributed to the study design, and read and approved the paper.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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