Harmful Mutation Load in the Mitochondrial Genomes of Cattle Breeds

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Research note

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Abstract

Objective

Domestication of wild animals results in a reduction in the effective population size and this could affect the deleterious mutation load of domesticated breeds. Furthermore, artificial selection will also contribute to accumulation deleterious mutations due to the increased rate of inbreeding among these animals. The process of domestication, founder population size, and artificial selection differ between cattle breeds, which could lead to a variation in their deleterious mutation loads. We investigated this using mitochondrial genome data from 252 animals belonging to 15 cattle breeds of the world.

Results

Our analysis revealed more than fivefold difference in the deleterious mutation load among cattle breeds. We also observed a negative correlation between the neutral heterozygosity and the ratio of amino acid changing diversity to silent diversity. This suggests a proportionally higher amino acid changing variants in breeds with low diversity. Our results highlight the magnitude of difference in the deleterious mutations present in the mitochondrial genomes of various breeds. The results of this study could be useful in predicting the rate of incidence of genetic diseases in different breeds.

Introduction

Domestication of wild animals result in a drastic reduction of effective population size as only a subsample of the wild population is used. Artificial selection further reduces the population size due to inbreeding within domesticated animals, which occurs during breed formation [1]. The reduction in the population size leads to the accumulation of deleterious variants as selection is not efficient in removing them owing to genetic drift in small populations [2]. Previous studies showed empirical evidence for these predictions by using the ratio (*w*) of diversity of amino acid replacement (nonsynonymous) polymorphisms and the diversity of silent (synonymous) polymorphisms as the measure of deleterious mutational load [3-6]. Since most of the replacement polymorphisms affect protein structure and function, they are harmful to the organism. In contrast silent polymorphisms are neutral – have no effect on proteins. Hence higher *w* suggests elevated deleterious mutation load. Earlier studies revealed a much higher *w* for domesticated pig, dog, rabbit, silkworm, rice and sunflower compared to their wild relatives [3-5, 7, 8]. Furthermore, the *w* estimated for different breeds of dogs were found to correlate with their silent diversity [5] and similar results were reported for the breeds of pig, rabbit and chicken [4]. Since the process of artificial selection, level of inbreeding and the number of founder animals used vary between cattle breeds, the harmful mutational load is also expected to differ among breeds. The present study is focused to investigate this by estimating the deleterious mutational load of the mitochondrial genomes of fifteen cattle breeds.

Methods

A total of 578 mitochondrial genomes of *Bos taurus* were downloaded from GenBank (https://www.ncbi.nlm.nih.gov/genbank/) by searching using the key words *Bos taurus*, *mitochondrion*, and *complete genome*. The records without a specific breed information were excluded. Furthermore, only the breeds that have mitochondrial genomes from more than five individuals were included and the mitogenomes that showed high population structure were excluded. This resulted in 252 mitogenomes. The number and accession numbers are given in Table S1.

Using in-house Perl scripts 13 mitochondrial protein-coding genes were extracted from the GenBank records using the annotations. Each protein-coding gene from 252 cattle were aligned using the program *mafft* [9]. After alignment all 13 protein-coding genes were to form a super alignment containing 11,229 base pairs from 252 animals. This alignment was then used to estimate silent (synonymous) and replacement (nonsynonymous) diversities using the Tajima method[10] employed in the software program MEGA [11]. For this purpose, we used the Pamilo-Bianchi-Li method [12, 13]. To estimate the variance, the bootstrap resampling procedure was utilized (using 100 replications). Pearson correlation coefficient was used to measure the strength and significance of correlations. However, using the nonparametric Spearman rank correlation also showed similar strength of correlations.

Results And Discussion

The complete mitochondrial genome sequences of 252 individuals belonging to 15 cattle breeds were obtained from GenBank (Supplementary Information - Table S1). The replacement and silent diversities were estimated for the concatenated alignment of 13 mitochondrial protein-coding genes and their ratio w were calculated. As shown in Figure 1, w varies more than fivefold (5.7) among cattle breeds with Brahman having the highest w of 0.66 and the lowest was observed for Iraqi (0.115). This suggests fivefold higher harmful mutations are segregating in Brahman cattle compared to their Iraqi counterparts. We then plotted w against the neutral (silent) diversity and found a highly significant negative correlation (Pearson $r = -0.77$, $P < 0.001$) (Figure 2). When population size declines, concomitant reduction in neutral diversity and elevation in the deleterious mutation load are expected based on theories [2]. Due this reason we observe a negative correlation between the two variables.

Our results highlight the magnitude of difference in the deleterious mutations present in the mitochondrial genomes of various breeds. Similar results were observed for the nuclear genes of pig, rabbit, chicken and dog breeds [4, 5]. In this study, the deleterious mutation loads of various breeds were determined based on nonsynonymous polymorphisms. However, a similar pattern is expected for the mutations causing major genetic diseases of cattle.

Conclusions

The present study revealed that the deleterious mutation load significantly varies between different cattle breeds. Hence the results of this study could be useful in predicting the rate of incidence of mitochondrial genetic diseases in various breeds.

Limitations

This study is based on mitochondrial genomes that are uniparentally inherited. Furthermore, recombination is not well documented in mitogenomes. Therefore, it is unclear whether a similar pattern of mutation load is expected in nuclear genomes. Hence, further studies based on large number of nuclear genomes is required to investigate this.

Abbreviations

MEGA: Molecular Evolutionary Genetic Analysis

Declarations

Acknowledgements

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Conflicts of Interests

The author declares that he has no conflicts of interests.

Availability of data and materials

The data used in this work can be obtained from GenBank using the list of accession numbers in the supporting table S1.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Author's contributions

SS – conceived the project, analysed data and wrote the paper.

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Figures

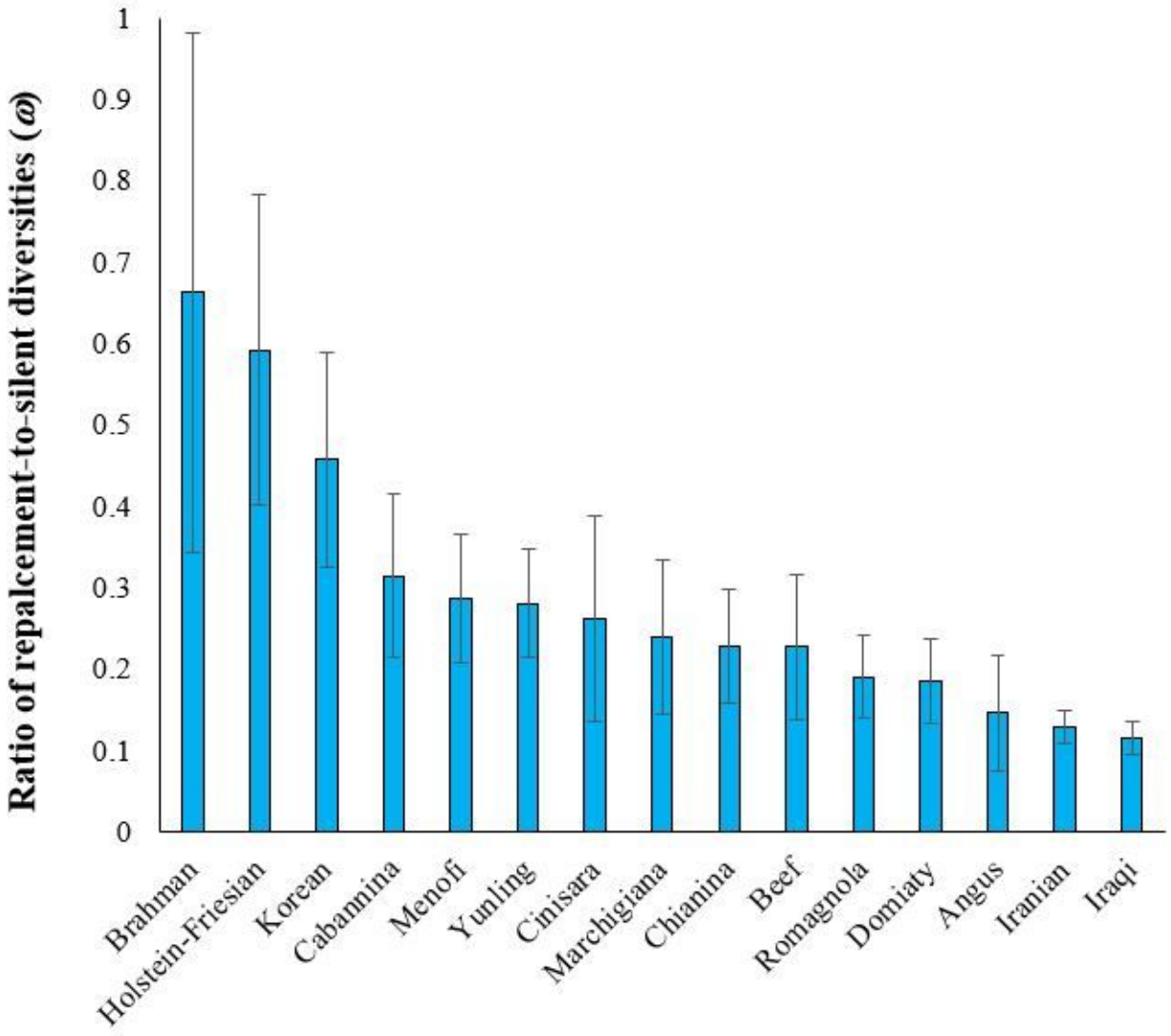

Figure 1

The ratio of replacement (nonsynonymous) diversity to silent (synonymous) diversity (ω) was estimated using 13 mitochondrial protein coding genes of 252 cattle belonging to 15 breeds. The error bars denote standard error of the mean that were estimated using the bootstrap resampling procedure (see Supplementary Methods).

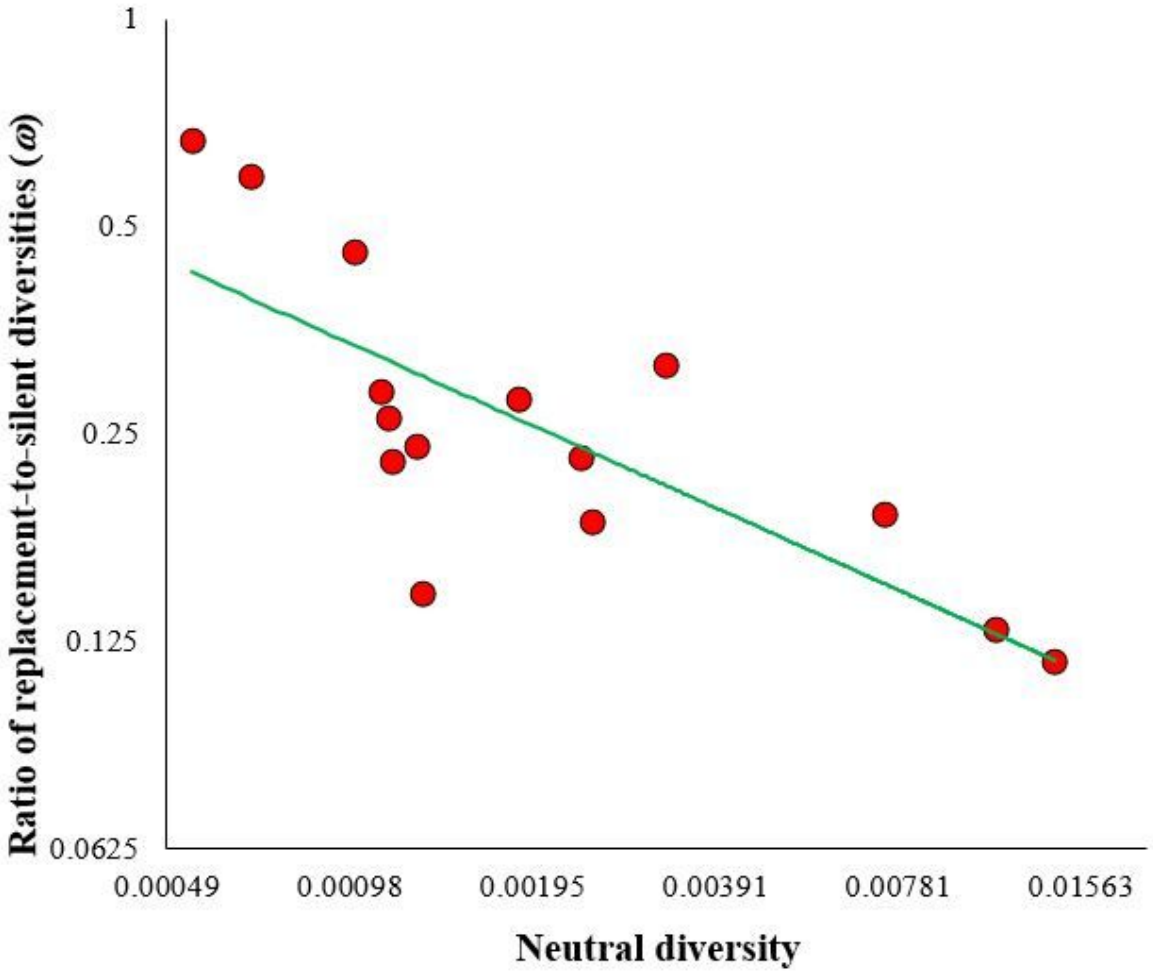

Figure 2

Relationship between neutral (synonymous) diversity and ω estimated for 15 cattle breeds. X and Y axes show log (base 2) transformed values. The correlation was highly significant (Pearson r = -0.77, P < 0.001). Best fitting regression line is shown.

Supplementary Files

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- SupportingInformation.pdf