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Short communication

Analysing the diversity of the caprine melanocortin 1 receptor (*MC1R*) in goats with distinct geographic origins

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ABSTRACT

In humans, the variability of the melanocortin 1 receptor (*MC1R*) gene has been associated with geography, being mainly determined by the amount of exposure to sunlight. Studies performed in pigs have also evidenced the existence of a geographic component in the distribution of *MC1R* haplotypes, probably as a consequence of an ancient split between Asian and European wild boars. Herewith, we have partially resequenced the caprine *MC1R* coding region in 58 goats from distinct geographic locations *i.e.* Colombia, Italy, Spain, France, Greece, Romania, Iran and Africa. The resulting dataset was merged with 39 previously published caprine *MC1R* sequences and a median joining network was built. This phylogenetic analysis did not yield any evidence of a relationship between geography and the clustering of caprine *MC1R* sequences, a result that was confirmed by performing a Mantel test with a previously published dataset of nine goat breeds (N = 319) with available *MC1R* genotypes. The majority of caprine *MC1R* variation was non-synonymous (c.676A > G, c.748G > T, c.764G > A and c.801C > G) and predicted to have functional effects. An analysis of goat *MC1R* sequences with the PAML 4 software provided evidence that two SNPs (c.764G > A and c.801C > G) might evolve under positive selection. The apparent lack of any link between caprine *MC1R* variation and geography might be explained by a complex array of factors including artificial selection for pigmentation phenotypes and recent divergence amongst goat breeds.

1. Introduction

Selection for coat color was probably implemented in ancient times as a consequence of religious beliefs and cultural preferences of livestock breeders (Zeder, 1994). For instance, the Book of Numbers establishes that red heifers need to be used in the purification rituals of people that have been in contact with a corpse, and black sheep were slaughtered in Chinese supplication ceremonies for rain

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because this color symbolizes water (Tao, 2007). Nonetheless, there were also practical reasons for selecting certain colors *e.g.* white wool is much easier to dye than the coloured one. In domestic animals, this process of selection contributed to generate a huge repertoire of pigmentation patterns that contrast strongly with the monochrome coat of their wild ancestors.

Pigmentation is a polygenic trait determined by a large number of loci (Sturm et al., 2001). The melanosomal protein complex is formed by tyrosinase, the enzyme that catalyses the synthesis of melanin, plus two other enzymes: tyrosinase-related proteins 1 and 2 (TYRP1 and TYRP2). Tyrosinase-related protein 2 catalyses the synthesis of 5,6-dihydroxyindole-2-carboxylic acid from DOPAchrome, which is converted to eumelanin by TYRP1 (Kondo and Hearing, 2011). Besides, both TYRP1 and TYRP2 contribute to the stabilization of tyrosinase (Sturm et al., 2001). Another key player in the determination of coat color is the melanocortin 1 receptor (*MC1R*) gene. Binding of this molecule, on the cell surface of melanocytes, by proopiomelanocortin (POMC) raises the levels of cAMP and activates tyrosinase, thus inducing the synthesis of black eumelanin (Sturm et al., 2001). The agouti-signaling protein (ASIP), that is also a ligand for MC1R, has the opposite effect i.e. by lowering the activation of tyrosinase promotes the synthesis of red/yellow pheomelanin (Makova and Norton, 2005; Parra, 2007).

In humans, *MC1R* diversity has been linked to geography and, more specifically, to the amount of sunlight exposure (Savage et al., 2008). This differential distribution is not only explained by drift and demographic factors, but also by natural selection. In this way, dark, eumelanin-rich photoprotective pigmentation is considered to be advantageous at tropical and equatorial latitudes because it is associated with a decreased rate of ultraviolet-induced folate degradation (Jablonski and Chaplin, 2010). In contrast, a light skin is favoured in geographic areas with reduced sunlight because it enhances the synthesis of vitamin D_3 (Jablonski and Chaplin, 2010).

Genetic diversity of livestock pigmentation genes has been less studied at an intercontinental scale than that of humans (Switonski et al., 2013). Remarkable differences in the distribution of *MC1R* haplotypes have been detected when comparing Chinese and European swine (Giuffra et al., 2000). Previous studies performed in goats characterized the diversity of the *MC1R* gene (Fontanesi et al., 2009; Nicoloso et al., 2012; Badaoui et al., 2014), but it was difficult to ascertain if it is associated with geography because only Italian and Spanish populations were sampled. In the current work, we aimed to investigate if there is a link between goat *MC1R* polymorphism and geography by analysing individuals from several locations covering a broad geographic range.

2. Materials and methods

2.1. Goat sampling

Blood samples were collected by jugular venipuncture from Colombian (N = 9), Italian (Sarda breed, N = 7), French (Saanen breed, N = 8), Iranian (Lori-Bakhtyari and Lori, N = 3), Greek (Youra breed, N = 2), Romanian (Carpathian breed, N = 7), Sahelian (N = 6) and Spanish (Majorcan breed, N = 8; Palmera breed, N = 8) goats (Supplementary Table S1). Sampling was performed by trained veterinarians in the context of sanitation campaigns and parentage controls not directly related with our research project. In all instances, veterinarians followed standard procedures and relevant international guidelines to ensure an appropriate animal care (ARRIVE guidelines, https://www.nc3rs.org.uk/arrive-guidelines; EU Directive 2010/63/EU for animal experiments). Genomic DNA was purified with the DNeasy Blood & Tissue Kit (Qiagen, Barcelona, Spain) and resuspended in ultrapure water.

2.2. Amplification and sequencing protocols

By using primers FW1, 5′-CCT GCA CTC CCC CAT GTA C-′3 and REV1, 5′-TGC GGA AGG CAT AAA TGA GG-3′, we amplified a fragment of approximately 0.7 kb of the *MC1R* gene that in previous studies was shown to contain most of its polymorphism (Fontanesi et al., 2009; Badaoui et al., 2014). Polymerase chain reactions were performed in a final volume of 15 μL containing 1.5 μL of 10 x PCR buffer, 2.5 mM $MgCl_2$, 0.3 μM of each primer, 0.25 mM of each dNTP, 0.75 U Taq Gold DNA polymerase (Applied Biosystem, Foster City, CA) and 50 ng genomic DNA. This reaction mixture was heated to 95 °C for 10 min, followed by 35 cycles of 95 °C for 1 min, 62 °C for 1 min and 72 °C for 1 min. Subsequently, a final extension step at 72 °C for 10 min was carried out. Amplification products were purified with the ExoSAP-IT PCR Cleanup kit (Affymetrix, Santa Clara, CA) and sequenced in both directions with primers FW2, 5′-ACC TGC TGG TGA GCG TCA G-3′ and REV1. Sequencing reactions were prepared with the Big Dye Terminator Cycle Sequencing Kit v1.1 (Applied Biosystems) and electrophoresed in an ABI 3730 DNA Analyzer (Applied Biosystems). Chromatograms were edited with the SeqScape software v2.5 (Applied Biosystems), and all sequences were submitted to the GenBank database (accession codes: KT071610-KT071667).

2.3. Phylogenetic and positive selection analyses

We carried out phylogenetic and statistical analyses by using our *MC1R* dataset plus 39 goat *MC1R* sequences (Supplementary Table S1) retrieved from GenBank (Badaoui et al., 2014). A median-joining network was built with the Network 4.6 software (Bandelt et al., 1999) by using default parameters. The codeml program of the PAML 4 package (Yang, 2007) was employed to detect positive selection. Maximum likelihood estimates of the *w*-ratio (d_N/d_S), *i.e.* the rate of non-synonymous substitutions per non-synonymous site (d_N) divided by the rate of synonymous substitutions per synonymous site (d_S), were obtained for each codon of the MC1R-encoding region under analysis. We contrasted models 7 (neutral model), which assumes a β-distribution for the *w*-ratio ($0 \leq w \leq 1$), with model M8 (selection model), which takes into account an extra category of sites with $w_1 > 1$ (positive selection). The performance of a likelihood ratio test, where twice the difference in the log-likelihood values corresponding to models 7 and 8 is compared with a χ^2 with two degrees of freedom, was used to assess the statistical significance of positive selection. Bayes Empirical Bayes inference was employed to determine the posterior probability that a given codon evolves under positive selection. We also performed a Mantel test (Mantel, 1967) to investigate if there is any relationship between geography and *MC1R* variation. In this way, we used a published dataset (Badaoui et al., 2014) of 319 goats genotyped for the c.673C > T, c.676A > G, c.748G > T, c.764G > A *MC1R* single nucleotide polymorphisms (SNPs). These goats belonged to the following breeds: Cilentana Nera (N = 26), Garganica (N = 41), Grigia Molisana (N = 13), Girgentana (N = 19), Malagueña (N = 43), Murciano-Granadina (N = 81), Tinerfeña (N = 38), Majorera (N = 20) and Palmera (N = 38). The Mantel test estimates the linear correlation between two matrices of the same rank, *i.e.* matrices of geographic (measured in km) and genetic (F_{ST} coefficient) distances, in order to find out if both parameters are associated (Mantel, 1967). We computed F_{ST} coefficients amongst these 9 breeds with the Genepop on the Web software (http://genepop.curtin.edu.au, Rousset, 2008). The Mantel test was carried out with the *XLSTAT* statistical package (https://www.xlstat.com/en).

Table 1
In silico prediction of the functional effects of goat *MC1R* polymorphisms with three softwares (SIFT, SNAP2 and MutPred) and detection of positively selected sites with PAML 4.

MC1R SNP	Amino acid change	SIFT	SNAP[2]	MutPred	PAML 4 $w = d_N/d_S$	PAML 4 Prob (BEB)[a]
c.673C > T	Q225X	Stop codon	Stop codon	Stop codon	–	–
c.676A > G	K226E	Not tolerated	Effect (score = 41)	0.491	4.69 ± 3.73	0.651
c.748G > T	F250V	Not tolerated	Effect (score = 70)	0.650	4.36 ± 3.71	0.609
c.764G > A	G255D	Not tolerated	Effect (score = 72)	0.647	6.54 ± 3.11	0.922
c.801C > G	C267W	Not tolerated	Effect (score = 81)	0.802	6.56 ± 3.10	0.924

[a] Posterior probability deduced with a Bayes Empirical Bayes approach.

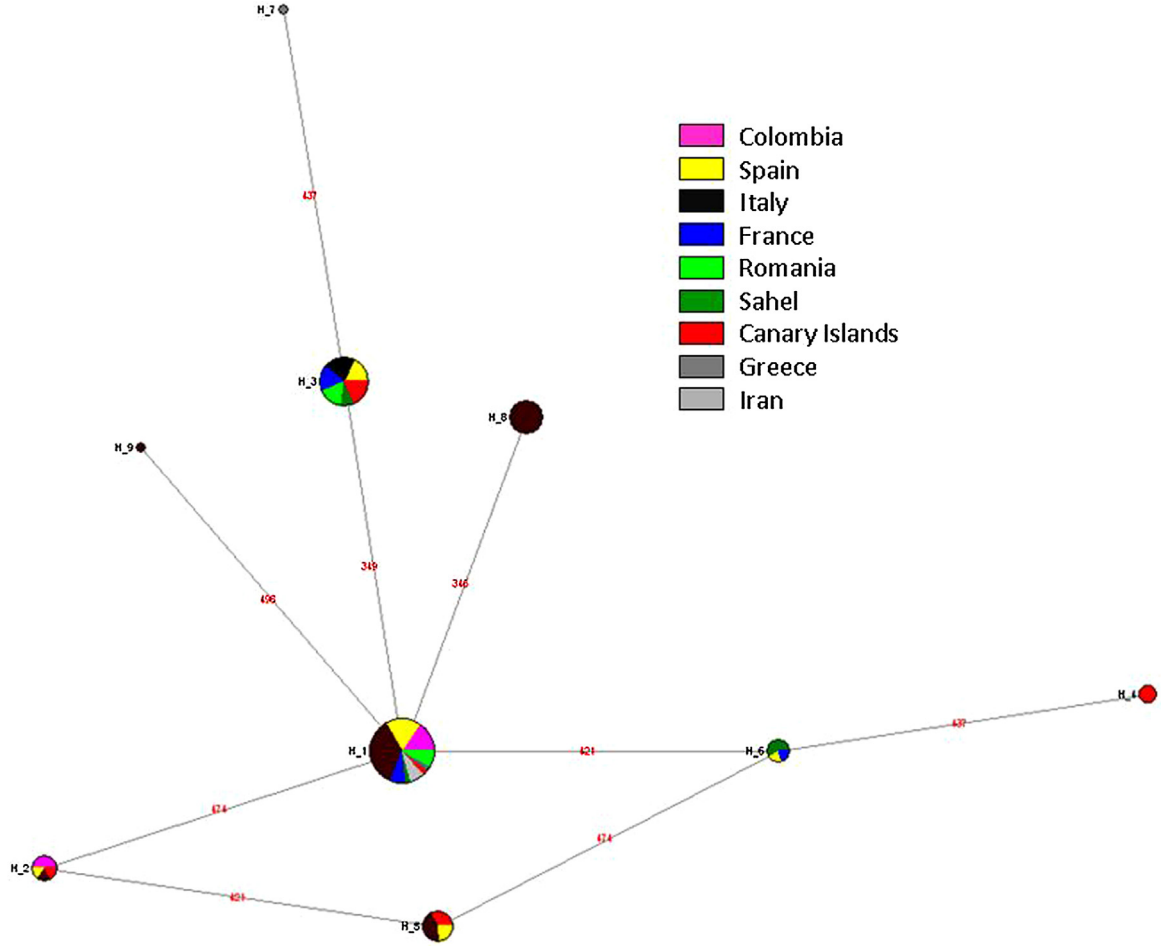

Fig. 1. Median joining network of *MC1R* sequences corresponding to Colombian, Spanish (Murciano-Granadina, Malagueña, Payoya, Mallorquina), Canarian (Palmera, Majorera, Tinerfeña), Italian (Sarda, Cilentana Nera, Derivata de Siria, Grigia Molisana, Maltese, Ionica, Girgentana, Garganica), French (Saanen), Greek (Youra), Iranian (Lori-Bakhtyari and Lori), Sahelian and Romanian (Carpathian) goats.

3. Results and discussion

By examining individuals with very distinct geographic origins, we expected to increase significantly the catalog of *MC1R* polymorphisms detected in goats. Nevertheless, we just found the set of five missense polymorphisms that were previously reported by Fontanesi et al. (2009), Nicoloso et al. (2012) and Badaoui et al. (2014), plus a silent mutation c.825C > T (Table 1, Supplementary Fig. S1). Four of the five polymorphic amino acid sites detected in goats happened to be variable when comparing the goat MC1R sequence with those of five additional mammalian species (Supplementary Fig. S2) The median joining network shown in Fig. 1 made evident that goats did not cluster according to their geographic origin. There was one main haplotype with a broad intercontinental distribution and several other *MC1R* haplotypes shared by individuals from distinct countries (Fig. 1, Supplementary Table S2). This pattern contrasts with the one observed in humans, where marked differences in *MC1R* allele frequencies between Asian, African and Caucasian populations exist, probably as a consequence of natural selection (eumelanin-rich pigmentation is photoprotective), genetic drift and other factors (Savage et al., 2008; Jablonski and Chaplin 2010). We also carried out of a Mantel test based on a dataset of 319 goats distributed in 9 populations and genotyped for 4 *MC1R* polymorphisms. As shown in Supplementary Fig. S3, the correlation between geographic and genetic distances was low (r = 0.244) and non-significant (*P*-value = 0.152). This result supports the absence of a detectable link between goat *MC1R* polymorphism and the geographic distribution of caprine breeds.

The type of variation that we and others (Fontanesi et al., 2009; Badaoui et al., 2014) have found in the caprine *MC1R* gene is quite particular of this locus. In this way, the vast majority of polymorphic sites are non-synonymous and *in silico* prediction tools as

SIFT (Kumar et al., 2009), SNAP[2] (Hecht et al., 2015) and MutPred (Li et al., 2009) indicate that they might have functional consequences (Table 1). In a study performed in pigs, Fang et al. (2009) also detected an excess of non-synonymous variation at the *MC1R* gene. One plausible explanation for this pattern of variation could be the occurrence of positive selection *i.e.* the systematic selection of mutations associated with coat color would have involved the loss of linked neutral variants. We tested this hypothesis by analysing our dataset of *MC1R* sequences with the codeml program of the PAML 4 package (Yang, 2007). The performance of a likelihood ratio test provided statistical support for the existence of positive selection ($P < 0.005$). Moreover, two codons with posterior probabilities above 0.90 were identified with the Bayes Empirical Bayes method (Table 1). This is consistent with previous reports, where evidences of positive selection acting on the *MC1R* gene of pigs (Fang et al., 2009) and cattle (Zhao et al., 2015; Xu et al., 2015) have been provided. Interestingly, in a previous study we determined that the genotypic frequencies of the caprine *MC1R* c.801C > G SNP are remarkably different in black and mahogany Murciano-Granadina goats (Zidi et al., 2012), a result that is consistent with data provided by Fontanesi et al. (2009). Moreover, we found that the genotypic frequencies of the c.764G > A polymorphism are significantly different in red and black Palmera goats, and that blonde and white Malagueña display different genotypic frequencies of the c.676A > G and c.748G > T SNPs when compared with their dark chestnut counterparts (Zidi et al., 2012).

The lack of detection of a tight link between caprine *MC1R* variation and geography is not unexpected because the effects of neutral forces on the variation of pigmentation genes can be counteracted, to some extent, by artificial selection for coat color. Indeed, breeds that are geographically close may have been selected for very different coat colors, whilst populations from distant locations may have been convergently selected for similar pigmentation phenotypes. Notably, the lack of correspondence between goat *MC1R* polymorphism and geography contrasts strongly with data evidencing that Chinese and European pigs carry different *MC1R* haplotypes (Fang et al., 2009). One possible explanation for this discrepancy would be that the quantitative effects of *MC1R* variation on coat color are not the same in goats and pigs, so the intensity of selection exerted on this locus would be also different in these two livestock species. Indeed, Fontanesi et al. (2009) presented several cases of incomplete associations between *MC1R* genotypes and pigmentation in goats. For instance, the protein-truncating mutation c.673C > T (Q225X) was highly associated with red color in the Girgentana breed, but in the Derivata de Siria breed, which is also red, only 15% of the individuals were homozygous for this polymorphism (Fontanesi et al., 2009). Similarly, the c.801C > G mutation was highly associated with the black *vs* mahogany color in Murciano-Granadina goats, while this relationship was less evident in the Maltese breed. According to Fontanesi et al. (2009), these observations may be explained by the existence of undetected mutations with regulatory effects on *MC1R* expression, genetic heterogeneity in the determination of coat color and the existence of epistatic interactions with other genes, such as *POMC* and *ASIP*, with strong effects on pigmentation patterns.

Another factor that may explain the differential MC1R genetic patterns observed in goats and pigs is the time of divergence. Modern goats descend from individuals domesticated at Eastern Anatolia 10,000 YBP (Naderi et al., 2008). In contrast, Far Eastern and Western wild boars diverged 1 Mya and they were independently domesticated in China and the Near East, respectively (Larson et al., 2005). In consequence, goat breeds diverged much more recently than Asian and European pigs, a feature that is expected to weaken the amount of genetic differentiation amongst populations distributed in different geographic locations.

4. Conclusions

The topology of the median-joining network based on goat *MC1R* sequences and the Mantel test did not provide evidence of a relationship between the variation of the caprine *MC1R* gene and geography, a result that can be explained by multiple demographic, biological and selection factors. Besides, we have obtained evidence that two codons in the goat *MC1R* gene might evolve under positive selection.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.smallrumres.2016.10.010.

References

Badaoui, B., Manunza, A., Castelló, A., D'Andrea, M., Pilla, F., Capote, J., Jordana, J., Ferrando, A., Martínez, A., Cabrera, B., Delgado, J.V., Landi, V., Gómez, M., Pons, A., El Ouni, M., Vidal, O., Amills, M., 2014. Technical note: advantages and limitations of authenticating Palmera goat dairy products by pyrosequencing the melanocortin 1 receptor (*MC1R*) gene. J. Dairy Sci. 97, 7293–7297.

Bandelt, H.J., Forster, P., Röhl, A., 1999. Median-joining networks for inferring intraspecific phylogenies. Mol. Biol. Evol. 16, 37–48.

Fang, M., Larson, G., Ribeiro, H.S., Li, N., Andersson, L., 2009. Contrasting mode of evolution at a coat color locus in wild and domestic pigs. PLoS Genet. 5, e1000341.

Fontanesi, L., Beretti, F., Riggio, V., Dall'Olio, S., González, E.G., Finocchiaro, R., Davoli, R., Russo, V., Portolano, B., 2009. Missense and nonsense mutations in melanocortin 1 receptor (*MC1R*) gene of different goat breeds: association with red and black coat colour phenotypes but with unexpected evidences. BMC Genet. 10, 47.

Giuffra, E., Kijas, J.M., Amarger, V., Carlborg, O., Jeon, J.T., Andersson, L., 2000. The origin of the domestic pig: independent domestication and subsequent introgression. Genetics 154, 1785–1791.

Hecht, M., Bromberg, Y., Rost, B., 2015. Better prediction of functional effects for sequence variants. BMC Genomics 16 (8), S1.

Jablonski, N.G., Chaplin, G., 2010. Colloquium paper: human skin pigmentation as an adaptation to UV radiation. Proc. Natl. Acad. Sci. U. S. A. 107 (Suppl (2)), 8962–8968.

Kondo, T., Hearing, V.J., 2011. Update on the regulation of mammalian melanocyte function and skin pigmentation. Exp. Rev. Dermatol. 6, 97–108.

Kumar, P., Henikoff, S., Ng, P.C., 2009. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat. Protoc. 4, 73–81.

Larson, G., Dobney, K., Albarella, U., Fang, M., Matisoo-Smith, E., Robins, J., Lowden, S., Finlayson, H., Brand, T., Willerslev, E., Rowley-Conwy, P., Andersson, L., Cooper, A., 2005. Worldwide phylogeography of wild boar reveals multiple centers of pig domestication. Science 307, 1618–1621.

Li, B., Krishnan, V.G., Mort, M.E., Xin, F., Kamati, K.K., Cooper, D.N., Mooney, S.D., Radivojac, P., 2009. Automated inference of molecular mechanisms of disease from amino acid substitutions. Bioinformatics 25, 2744–2750.

Makova, K., Norton, H., 2005. Worldwide polymorphism at the *MC1R* locus and normal pigmentation variation in humans. Peptides 26, 1901–198.

Mantel, N., 1967. The detection of disease clustering and a generalized regression approach. Cancer Res. 27, 209–220.

Naderi, S., Rezaei, H.R., Pompanon, F., Blum, M.G., Negrini, R., Naghash, H.R., Balkiz, O., Mashkour, M., Gaggiotti, O.E., Ajmone-Marsan, P., Kence, A., Vigne, J.D., Taberlet, P., 2008. The goat domestication process inferred from large-scale

mitochondrial DNA analysis of wild and domestic individuals. Proc. Natl. Acad. Sci. U. S. A. 105, 17659–17664.
Nicoloso, L., Negrini, R., Ajmone-Marsan, P., Crepaldi, P., 2012. On the way to functional agro biodiversity: coat colour gene variability in goats. Animal 6, 41–49.
Parra, E.J., 2007. Human pigmentation variation: evolution, genetic basis, and implications for public health. Am. J. Phys. Anthropol., 85–105.
Rousset, F., 2008. Genepop'007: a complete reimplementation of the Genepop software for Windows and Linux. Mol. Ecol. Res. 8, 103–106.
Savage, S.A., Gerstenblith, M.R., Goldstein, A.M., Mirabello, L., Fargnoli, M.C., Peris, K., Landi, M.T., 2008. Nucleotide diversity and population differentiation of the melanocortin 1 receptor gene, *MC1R*. BMC Genet. 9, 31.
Sturm, R.A., Teasdale, R.D., Box, N.F., 2001. Human pigmentation genes: identification, structure and consequences of polymorphic variation. Gene 277, 49–62.
Switonski, M., Mankowska, M., Salamon, S., 2013. Family of melanocortin receptor (*MCR*) genes in mammals-mutations, polymorphisms and phenotypic effects. J. Appl. Genet. 54, 461–472.
Tao, W., 2007. Shang ritual animals: colour and meaning (part 1). B. Sch. Orient. Afr. St. 70, 305–372.
Xu, L., Bickhart, D.M., Cole, J.B., Schroeder, S.G., Song, J., Tassell, C.P., Sonstegard, T.S., Liu, G.E., 2015. Genomic signatures reveal new evidences for selection of important traits in domestic cattle. Mol. Biol. Evol. 32, 711–725.
Yang, Z., 2007. PAML 4: phylogenetic analysis by maximum likelihood. Mol. Biol. Evol. 24, 1586–1591.
Zeder, M.A., 1994. Of kings and shepherds: specialized animal economy in UR III Mesopotamiae. In: Stein, G., Rothman, M. (Eds.), Chiefdoms and Early States in the Near East: the Organizational Dynamics of Complexity. Prehistory Press, Madison, pp. 175–191.
Zhao, F., McParland, S., Kearney, F., Du, L., Berry, D.P., 2015. Detection of selection signatures in dairy and beef cattle using high-density genomic information. Genet. Sel. Evol. 47, 49.
Zidi, A., Badaoui, B., Manunza, A., Serradilla, J.M., Capote, J., Urrutia, B., Carrizosa, J., Pilla, F., D'Andrea, M.S., Jordana, J., Ferrando, A., Pons, A., Sánchez, A., Landi, V., Gómez, M., Martínez, A., Vidal, O., Amills, M., 2012. Mutations at the caprine *MC1R* gene are associated with coat color in Spanish goats. In: 11th International Conference on Goats, Gran Canaria, Spain.