BRIEF NOTES

Identification of positively selected sites in the goat kappa casein (CSN3) gene

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Background: Analysis of the rates of non-synonymous vs. synonymous substitutions ($w = dN/dS$) in the kappa casein (CSN3) genes of Bovidae has provided evidence that positive selection has accelerated amino acid divergence of this protein.¹ The goat CSN3 gene is extraordinarily polymorphic, with sixteen alleles identified to date.² A significant part of this genetic variation is non-synonymous, suggesting that positive selection might have been a driving force shaping the allelic repertoire of this gene. Moreover, there is evidence that these CSN3 variants have differential effects on dairy traits.³ Herewith, we have used codon-based substitution models to identify and characterize with high resolution the footprint of positive selection in the goat CSN3 gene.

Analysis of positive selection: Sequence data employed in our analysis are listed in Table S1. Positively selected codons were identified by using the codeml program, which is integrated in the paml 3.15 package.⁴ A detailed description of the models and test of significance is reported in Appendix S1. The global w value of the goat CSN3 gene was significantly greater than one ($P < 0.01$), a feature indicative of positive selection. In contrast, a distance-based analysis with the mega 3.1 software did not yield significant results (data not shown). Analysis with paml 3.15 identified three codons (p.Gln65Arg, p.Val86Ile and Asp111Gly, reference sequence: CAA43174) displaying suggestive evidence of positive selection (posterior probability > 0.90 , Table S2). Large standard deviations in mean estimates of w might be likely attributable to the fact that the sequence dataset was rather small. Moreover, chance variation in the mutation pattern across sites can produce false positives in this kind of test,⁵ so further studies will be needed to confirm our results. Amongst the three identified codons, p.Gln65Arg appeared to be particularly interesting because both PMUT and Polyphen indicated that this substitution might alter protein function (Table S2). The biological meaning of positive selection at the CSN3 loci of Bovidae has not been fully elucidated.¹ Interestingly, CSN3 bioactive peptides play an important role in gastrointestinal mucosal immunity and they have antithrombotic and antihypertensive properties.^{6, 7} In consequence, positive selection at CSN3 might affect biological fitness in the context of any of these physiological processes.