Received: 18 January 2022 | Accepted: 18 January 2022

DOI: 10.1111/age.13177

ANIMAL GENETICS WILEY

BRIEF REPORT

# Evaluation of truncating variants in the *LCORL* gene in relation to body size of goats from Switzerland

## BACKGROUND

More than 200 years ago, the formation of goat breeds began through morphological standardisation, especially of coat colour and body size, and systematic selection to improve production traits (Burren et al., 2016). In Switzerland, breed formation, followed by various breeding objectives and selection programmes, resulted in 10 modern goat breeds (Henkel et al., 2019). Recently, the VarGoats project generated individual whole genome sequencing data from representatives of these Swiss breeds beside 116 further *Capra hircus* breeds, including the Boer goat originating from Africa, to understand the consequences of domestication and breeding (Denoyelle et al., 2021).

Variation in stature or body size in domestic animals such as cattle or dogs is generally controlled by fewer genes with greater effects than in humans (Bouwman et al., 2018; Plassais et al., 2019). The *ligand-dependent nuclear receptor corepressor-like* gene (*LCORL*) gene encoding a transcription factor has been repeatedly found to be associated with measures of skeletal frame size and adult height in humans and dogs (Plassais et al., 2019; Soranzo et al., 2009). Alternative splicing results in multiple *LCORL* transcript variants. Similar to humans, in goats, one transcript is long encoding isoform X1 (1864 aa, XP_017904811.1) and several that are significantly shorter (e.g. 601 aa, XP_017904814.1), differing significantly in the sequence of the last exons. Alignment of the human (NP_001381375.1) and caprine (XP_017904811.1) LCORL protein sequences revealed a strong 82% match. Recently, a search for signatures that are shared across large-sized goat breeds revealed that five medium-to-large-sized Pakistani goat breeds had a common selection signature on chromosome 6 in a region harbouring the *LCORL* gene (Saif et al., 2020). Subsequent sequencing analyses proposed a frameshift variant in *LCORL* exon 7 (p.Ser277fs) as potentially causal variant mediating the body size-increasing effect (OMIA 002246-9925). The long LCORL isoform X1 contains a DUF4553 DNA-binding domain from amino acid position 1404 to 1860 within the deleted segment of the derived caprine allele. Due to strong conservation of this DNA-binding domain across mammals it could be speculated that, in large goats, the truncation may disrupt transcription factor binding of LCORL with its target. The same was reported for dogs, as a single nucleotide insertion in the last exon of the long isoform of *LCORL*, resulting in a premature stop codon after amino acid 1221 and a significantly truncated protein, has never observed small breeds, whereas it is present in medium and large breeds (OMIA 002246-9615) (Plassais et al., 2019).

## OWN ANALYSIS

Since the p.Ser277fs variant was noticed before in whole-genome sequence data of Boer goats, the first objective of this study was to conduct a body size association study in this breed to test the hypothesis regarding the previously postulated effect on height. Secondly, we evaluated five additional truncating variants located in the same *LCORL* exon in relation to body size, that were found within the VarGoats project variant catalogue in individuals of Swiss goat breeds: p.Leu539fs in Grisons Striped (BST), p.Ala663fs and p.Phe1486fs in Chamois Colored (GFG), p.Arg1089* in Nera Verzasca (NER) and Peacock (PFA), and p.Glu1457fs in Saanen (SAN) goats (Table S1). Except for the two variants found in SAN, NER, and PFA, four frameshift variants, including the p.Ser277fs and p.Phe1486fs variants, that both were also found in Boer (BUR) goats, occurred at low frequencies also in various other breeds (Table S1).

Subsequently we genotyped a total of 717 female goats older than 12 months, including a cohort of 190 BUR from Switzerland as well as cohorts of five different Swiss goat breeds (140 BST, 110 GFG, 151 SAN, 32 NER, 94 PFA) for the respective *LCORL* variants (Table S2). Genomic DNA was extracted from EDTA blood samples. PCR and Sanger sequencing were used to perform genotyping of the *LCORL* variants on an ABI3730 capillary sequencer (Table S1).

To study possible association with body size, phenotypes for five different measured traits (withers height, body length, flank depth, pelvis width, pelvis length) for all 717 goats were obtained (Figure S1, Table S2).

Statistical analysis was performed with R-packages sjPlot, sjmisc, sjlabelled, multcompView, ggpubr, and emmeans. The following multivariate linear model using the restricted maximum likelihood procedure was applied to estimate the body masses body length, flank depth, pelvic width, and pelvic length: $y_{ijk} = \mu + L_i + \text{age}_j + \text{height}_k + e_{ijk}$ ($y_{ijk}$ = consecutive observation on body size; $\mu$ = overall mean; $L_i$ = fixed effect of *L* (examined *LCORL* variant); $\text{age}_j$ = fixed effect of age at measurement; $\text{height}_k$ = fixed effect of withers height; $e_{ijk}$ = random residual). The variable withers height is both response variable and covariate. For the response variable withers height, the same model was used without withers height as a covariate: $y_{ijk} = \mu + L_i + \text{age}_j + e_{ij}$.

In the studied Boer population, the alleles at both variants studied segregate in almost perfect linkage disequilibrium at high frequencies (0.40 and 0.59). Analysis of the relationship between the data measuring five different traits and the two variants revealed no significant difference between *LCORL* genotypes and body size (Figure S2, Table S3).

The breed-specific *LCORL* variant of Saanen as well as the variant studied in Grisons Striped goats showed a moderate frequency of 0.28 and 0.17, respectively (Table S3). In contrast, the respective genotyped *LCORL* variants in the other three Swiss breeds (GFG, NER, PFA) were found with frequencies below 10% for the derived alleles, resulting in an overrepresentation of the wild type genotypes and only few heterozygous and almost no homozygous animals in the studied cohorts (Table S3). Therefore, for two variants in BST and GFG goats where only single homozygotes for the derived allele were detected these animals were combined with the heterozygotes in a single group for the statistical analysis. Similar to what was found in Boer goats, no significant association was revealed in GFG and SAN, except a possible genotype–phenotype relation of the p.Glu1457fs variant on withers height in Saanen goats (Table S3). Although only five animals homozygous for the derived allele in total, these were obviously larger compared to the two remaining genotypes (Figure S2). Similar significant differences were noticed for the frameshift variant p.Leu539fs in regard to four out of five body size traits in Grisons Striped (BST), as well as for the nonsense variant p.Arg1089* and withers height in Nera Verzasca and Peacock goat (Table S3).

## CONCLUSIONS

This follow-up study aimed to investigate the previously postulated possible association between truncating variants in the *LCORL* gene and larger body size in goats. We have clearly shown that body size in Boer goat is obviously not associated with the frameshift variant previously found in large-sized Pakistani goat breeds, nor with a second *LCORL* frameshift variant studied. However, we found suggestive evidence of genotype–phenotype association for three other breed-specific truncating variants in the *LCORL* with withers height and other body size traits in selected cohorts of four different local Swiss goat breeds. Due to the small sample size and the low to moderate frequency of variant alleles, we consider these results preliminary before claiming causality. Nevertheless, these initial results in Swiss goats support the evidence previously shown in dogs for a direct effect on stature due to loss-of-function variants leading to the absence of the functionally important DNA-binding domain of the long LCORL isoform. Therefore, the research should continue with enlarged cohorts of well-phenotyped animals.

## ACKNOWLEDGEMENTS

We would like to thank all participating farmers as well as the national breeding association (Schweizerischer Ziegenzuchtverband, SZZV, namely Erika Bangerter) and the Swiss-Boer - Verein Schweizerische Burenziegen for their support. We thank Nathalie Besuchet-Schmutz for expert technical assistance. The Swiss Federal Office of Agriculture (OFAG) is acknowledged for the financial support of the study.

## DATA AVAILABILITY STATEMENT

The data supporting the findings of this study can be found in the electronic appendix (supporting information) of this publication. Further details are available from the corresponding author upon reasonable request.

Jennifer Kalinka Graber[1]
Heidi Signer-Hasler[2]
Alexander Burren[2]
Cord Drögemüller[1]

[1]*Institute of Genetics, Vetsuisse Faculty, University of Bern, Bern, Switzerland*
[2]*School of Agricultural, Forest and Food Sciences, Bern University of Applied Sciences, Zollikofen, Switzerland*

**Correspondence**
Cord Drögemüller, Institute of Genetics, Vetsuisse Faculty, University of Bern, Bern 3012, Switzerland.
Email: cord.droegemueller@vetsuisse.unibe.ch

## ORCID

*Heidi Signer-Hasler* https://orcid.org/0000-0001-5193-5306
*Cord Drögemüller* https://orcid.org/0000-0001-9773-522X

## REFERENCES

Bouwman, A.C., Daetwyler, H.D., Chamberlain, A.J., Ponce, C.H., Sargolzaei, M., Schenkel, F.S. et al. (2018) Meta-analysis of

genome-wide association studies for cattle stature identifies common genes that regulate body size in mammals. *Nature Genetics*, 50, 362–367.

Burren, A., Neuditschko, M., Signer-Hasler, H., Frischknecht, M., Reber, I., Menzi, F. et al. (2016) Genetic diversity analyses reveal first insights into breed-specific selection signatures within Swiss goat breeds. *Animal Genetics*, 47, 727–739.

Denoyelle, L., Talouarn, E., Bardou, P., Colli, L., Alberti, A., Danchin, C. et al. (2021) VarGoats project: a dataset of 1159 whole-genome sequences to dissect *Capra hircus* global diversity. *Genetics Selection Evolution*, 53, 1–14.

Henkel, J., Saif, R., Jagannathan, V., Schmocker, C., Zeindler, F., Bangerter, E. et al. (2019) Selection signatures in goats reveal copy number variants underlying breed-defining coat color phenotypes. *PLoS Genetics*, 15, 1–18.

Plassais, J., Kim, J., Davis, B.W., Karyadi, D.M., Hogan, A.N., Harris, A.C. et al. (2019) Whole genome sequencing of canids reveals genomic regions under selection and variants influencing morphology. *Nature Communications*, 10, 1–14.

Saif, R., Henkel, J., Jagannathan, V., Drögemüller, C., Flury, C., Leeb, T. et al. (2020) The LCORL locus is under selection in large-sized Pakistani goat breeds. *Genes (Basel)*, 11, 1–10.

Soranzo, N., Rivadeneira, F., Chinappen-Horsley, U., Malkina, I., Richards, J.B., Hammond, N. et al. (2009) Meta-analysis of genome-wide scans for human adult stature identifies novel loci and associations with measures of skeletal frame size. *PLoS Genetics*, 5, e1000445.

## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Graber, J.K., Signer-Hasler, H., Burren, A. & Drögemüller, C. (2022) Evaluation of truncating variants in the *LCORL* gene in relation to body size of goats from Switzerland. *Animal Genetics*, 00, 1–3. Available from: https://doi.org/10.1111/age.13177