Received: 28 August 2018 | Accepted: 16 January 2019

DOI: 10.1111/jvim.15431

Journal of Veterinary Internal Medicine Open Access

ACVIM American College of Veterinary Internal Medicine

CASE REPORT

Hereditary xanthinuria in a goat

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Funding information
National Institutes of Health, Grant/Award Number: 1K01OD019912-03

A 2-year-old mixed breed goat was presented for a 1-day history of anorexia and 1 week of weight loss. Serum biochemistry disclosed severe azotemia. Abdominal ultrasound examination showed decreased renal corticomedullary distinction, poor visualization of the renal pelves, and dilated ureters. On necropsy, the kidneys were small, the pelves were dilated, and the medulla was partially effaced by variably sized yellow nephroliths. Histologically, cortical and medullary tubules were distended by yellow-brown, multilayered crystals. Stone composition was 100% xanthine. Exonic sequencing of xanthine dehydrogenase (*XDH*) and molybdenum cofactor sulfurase (*MOCOS*) identified 2 putative pathogenic variants: a heterozygous *XDH* p.Leu128Pro variant and a homozygous *MOCOS* p.Asp303Gly variant. Variant frequencies were determined in 7 herd mates, 12 goats undergoing necropsy, and 443 goats from genome databases. The *XDH* variant was not present in any of these 462 goats. The *MOCOS* variant allele frequency was 0.03 overall, with 3 homozygotes detected. Hereditary xanthinuria is a recessive disorder in other species, but the *XDH* variant could be causal if the case goat is a compound heterozygote harboring a second variant in a regulatory region not analyzed or if the combination of the *XDH* and *MOCOS* variants together abolish XDH activity. Alternatively, the *MOCOS* variant alone could be causal despite the presence of other homozygotes, because hereditary xanthinuria in humans often is asymptomatic. Ours is the first report describing the clinical presentation and pathology associated with xanthine urolithiasis in a goat. The data support hereditary xanthinuria, but functional studies are needed to conclusively determine the causal variant(s).

KEYWORDS

caprine, kidney, MOCOS, urinary system, urolith, xanthine

1 | CASE DESCRIPTION

A 2-year-old, female, Boer mix goat was presented for a 1-day history of anorexia and 1 week of severe weight loss. The doe's diet consisted of coastal hay and pasture supplemented with unspecified commercial goat pellets. The doe historically was reported to be smaller than the remaining herd mates. On physical examination, the doe was dull, unable to stand and emaciated. Rectal temperature was 97.0°F, heart rate was 70 bpm, and respiration was 20 rpm. The oral mucous membranes were tacky and pale. Assessment of the mucous membranes yielded a score of 5 using the FAMACHA system,[1] which is used to clinically assess anemia in sheep and goats, particularly associated with infection with *Haemonchus contortus*. Complete blood count identified a hematocrit of 19% (reference interval [RI], 22%-38%), total protein concentration of 7.2 g/dL (RI, 6.4-7.0 g/dL), and an inflammatory leukogram. Serum biochemistry disclosed an increased BUN (223 mg/dL, RI, 10-20 g/dL) and creatinine concentrations (4.7 mg/dL; RI, 1.0-1.8 mg/dL). Abdominal ultrasound examination showed bilaterally decreased renal corticomedullary distinction with poor visualization of the renal pelves and dilated ureters. The goat died spontaneously after the procedure, and the carcass was submitted for necropsy.

Grossly, the kidneys were moderately small, pale, firm and gritty. The renal pelves were severely dilated by variably-sized, gravel-like, yellow nephroliths. Numerous fine, granular, yellow nephroliths were embedded within the markedly atrophied medulla (Figure 1). Additional unrelated

Abbreviations: MOCOS, molybdenum cofactor sulfurase; RI, reference interval; XDH, xanthine dehydrogenase.

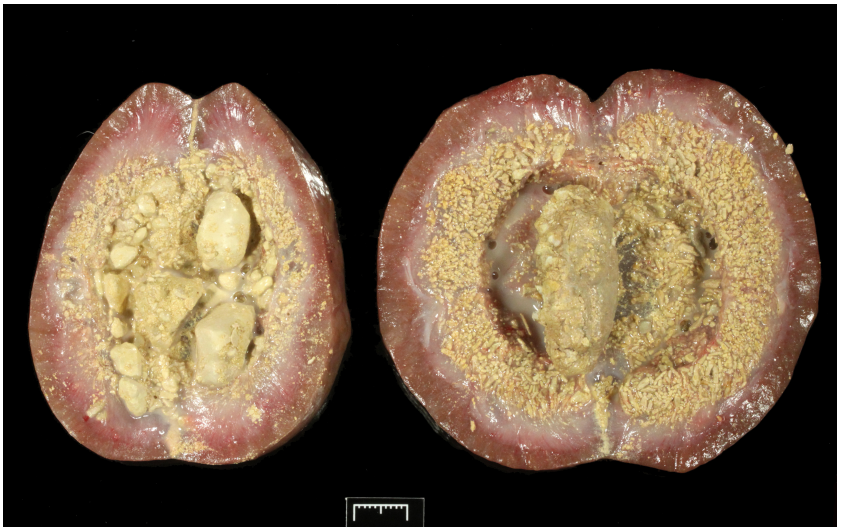

FIGURE 1 Kidneys, goat. Numerous variably sized, yellow nephroliths filled the dilated renal pelves and were embedded in the atrophied medulla. Bar is 1 cm

gross findings included pericardial and marrow serous atrophy of fat, abomasal haemonchosis, and pericardial effusion. Histologically, the renal medulla was replaced by abundant mineral concretions (Figure 2A). The majority of the cortical and medullary tubules were distended by yellow-brown, multilayered crystals (Figure 2B). The remaining tubules were either ruptured or atrophied, with degeneration and regeneration of the renal tubular epithelium. The interstitium was replaced by abundant fibrous connective tissue and infiltrated by lymphocytes, plasma cells, fewer macrophages, and occasional multinucleated giant cells. Glomerular tufts occasionally were sclerotic. A chronic polypoid cystitis with Brunner's nests and a focal luminal cystolith were present in the bladder.

To determine the identity of the nephroliths, samples were evaluated by infrared spectroscopy by the Minnesota Urolith Center and identified as 100% xanthine. The primary etiologies of xanthine urolithiasis reported in other species, such as humans and dogs, are genetic inborn errors of metabolism (hereditary xanthinuria) or treatment with a xanthine oxidase inhibitor (iatrogenic xanthinuria).[2–4] In the absence of a history of xanthine oxidase inhibitor use, it was suspected that xanthine nephrolithiasis in this case was caused by hereditary xanthinuria. To test this hypothesis, genomic DNA was extracted from the liver using a commercial kit (Gentra Puregene Blood Kit; Qiagen Sciences, Germantown, Maryland). Sanger sequencing was performed for all coding regions of *XDH* and *MOCOS*, the 2 genes responsible for hereditary xanthinuria types I and II, respectively.[1] Primers were designed using Primer3 (Primer3web, version 4.1.0; http://bioinfo.ut.ee/primer3/) and the NCBI *Capra hircus* reference genome (assembly ARS1/ASM170441v1); the primer sequences are provided in Supplementary Table 1. The goat had both homozygous and heterozygous *XDH* variants (consistent with 2 diverse haplotypes). She was homozygous for all variants identified in *MOCOS* (consistent with a single haplotype). Variants were annotated based on the goat NCBI protein reference sequences NP_001272553.1 (XDH) and XP_017894905.1 (MOCOS). Ten homozygous variants (5 missense and 5 synonymous) and 7 heterozygous variants (1 missense and 6 synonymous) were identified that were distinct from the reference genome (Table 1).

Potential pathogenicity of the missense variants was evaluated using 3 prediction programs: (1) SIFT scores (derived with the Variant Effect Predictor),[5,6] a tool that evaluates alignment in the protein family

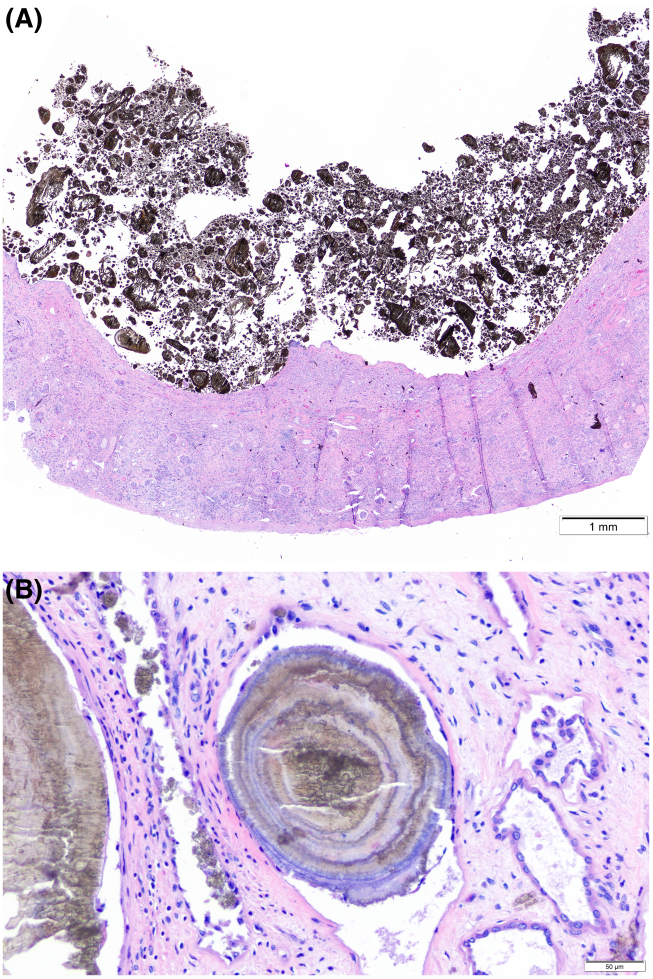

FIGURE 2 A, Kidney, goat. The renal medulla was replaced by abundant nephroliths with compression of the adjacent renal parenchyma. Hematoxylin and eosin (H&E). B, Kidney, goat. Renal tubules were distended by brown, multilayered crystals. H&E

TABLE 1 Seventeen exonic *XDH* and *MOCOS* variants found in a goat with xanthine urolithiasis

		Pathogenicity prediction scores			Herdmates		Necropsy goats		NextGen and VarGoats projects		All control and database goats	
Variant	**Effect**	**SIFT**	**PROV**	**MutPred2**	**AF**	**HOMF, #/Total**	**AF**	**HOMF, #/Total**	**AF**	**HOMF, #/Total**	**AF**	**HOMF, #/Total**
XDH												
Homozygous												
Chr11:14068793C>T	p.Gly399Asp	0.06	0.85	0.27	0.93	0.86, 6/7	0.04	0, 0/12	0.03	0.002, 1/443	0.04	0.02, 7/462
Chr11:14068751C>T	p.Arg413Lys	0.48	−0.11	0.15	0.93	0.86, 6/7	0.04	0, 0/12	0.03	0.002, 1/443	0.04	0.02, 7/462
Chr11:14066462G>A	p.Cys436	n/a	n/a	n/a	0.88	1.00, 7/7	0.80	0.60, 6/10	0.68	0.50, 221/438	0.68	0.51, 234/455
Chr11:14031736A>G	p.Arg1280	n/a	n/a	n/a	1.00	1.00, 7/7	1.00	1.00, 12/12	0.96	0.92, 407/443	0.96	0.92, 426/462
Chr11:14031637C>T	p.Lys1313	n/a	n/a	n/a	1.00	1.00, 7/7	1.00	1.00, 12/12	0.93	0.91, 403/443	0.93	0.91, 422/462
Heterozygous												
Chr11:14084297A>G	**p.Leu128Pro**	**0**	**−6.36**	**0.96**	**0**	**0, 0/7**	**0**	**0, 0/12**	**0**	**0, 0/443**	**0**	**0, 0/462**
Chr11:14071619T>C	p.Thr324	n/a	n/a	n/a	0.83	0.67, 4/6	0	0, 0/12	0.02	0.002, 1/440	0.03	0.01, 5/458
Chr11:14071601G>A	p.Val330	n/a	n/a	n/a	0.83	0.67, 4/6	0	0, 0/12	0.02	0.002, 1/441	0.03	0.01, 5/459
Chr11:14070246A>G	p.Ser368	n/a	n/a	n/a	0.29	0, 0/7	0.72	0.36, 4/11	0.55	0.39, 172/438	0.55	0.39, 176/456
Chr11:14055384G>C	p.Ala584	n/a	n/a	n/a	0.79	0.57, 4/7	0.04	0, 0/12	0.07	0.02, 7/440	0.08	0.02, 11/459
Chr11:14055351G>A	p.Asp595	n/a	n/a	n/a	0.79	0.57, 4/7	0.08	0, 0/12	0.09	0.02, 7/442	0.04	0.02, 11/461
Chr11:14051915G>A	p.Ile697	n/a	n/a	n/a	0.79	0.57, 4/7	0.08	0, 0/12	0.08	0.03, 14/440	0.09	0.04, 18/459
MOCOS												
Homozygous												
Chr24:21240288A>G	p.Val228Ala	0.78	−0.43	0.18	0.93	0.86, 6/7	1.00	1.00, 12/12	0.87	0.79, 195/248	0.88	0.80, 213/267
Chr24:21240063T>C	**p.Asp303Gly**	**0.03**	**−2.06**	**0.48**	**0.07**	**0, 0/7**	**0.04**	**0, 0/12**	**0.03**	**0.007, 3/443**	0.03	0.006, 3/462
Chr24:2124004 1C>G	p.Glu310Asp	0.58	−0.98	0.25	0.29	0, 0/7	0.73	0.64, 7/11	0.66	0.48, 211/442	0.67	0.47, 218/460
Chr24:21220297T>C	p.Gly610	n/a	n/a	n/a	0.83	0.67, 4/6	0.05	0, 0/11	0.18	0.09, 38/441	0.19	0.09, 42/458
Chr24:21220258A>G	p.Asn623	n/a	n/a	n/a	1.00	1.00, 7/7	1.00	1.00, 11/11	0.90	0.82, 204/248	0.91	0.83, 222/266

Variant effect positions refer to the NCBI goat protein reference sequences NP_001272553.1 (XDH) and XP_017894905.1 (MOCOS).
SIFT, PROVEAN, and MutPred2 scores were used to predict pathogenicity for missense variants. For SIFT, scores range from 0 to 1; those ≤0.05 are predicted to be deleterious. For PROVEAN, scores ≤−2.5 are predicted to be deleterious. For MutPred2, scores range from 0 to 1; those ≥0.5 are predicted to be deleterious. Bold font indicates the putative causal variant for xanthinuria in the goat.
Abbreviations: AF, allele frequency; HOMF, homozygote frequency; n/a, not applicable; PROV, PROVEAN.

and type of amino acid change to predict pathogenicity, (2) PROVEAN,[7] which also uses an alignment-based approach, and (3) MutPred2,[8,9] a tool that uses a random forest model to predict effects on protein structure and function and to infer pathogenicity. Two of the missense variants were predicted to be pathogenic (Table 1): a heterozygous *XDH* p.Leu128Pro variant (chr11:14084297A>G) and a homozygous *MOCOS* p.Asp303Gly variant (chr24:21240063T>C). The *XDH* p.Leu128Pro variant passed the threshold scores for pathogenicity for all 3 prediction programs. The *MOCOS* p.Asp303Gly variant reached the SIFT score threshold for pathogenicity and had scores close to, but not achieving, the threshold for pathogenicity with PROVEAN and MutPred2. With InterPro, a program that analyzes proteins to classify them into families and predict protein domains and other important protein sites, we found that both variants lie within protein domains: *XDH* p.Leu128Pro is within the Fe/S binding domain (IPR002888, amino acids 87-159) and *MOCOS* p.Asp303Gly is within an aminotransferase class V domain (IPR028886, amino acids 50-481).[10]

We next evaluated conservation at the residues corresponding to the caprine *XDH* 128 and *MOCOS* 303 positions. Sequence was aligned for vertebrate species using the Multiz alignment track of the University of California, Santa Cruz Genome Browser.[11] Alignment data for both residues is presented in Supplementary Table 2. Ninety-eight species were available for the *XDH* 128 residue, and all had leucine as the reference amino acid. Ninety-seven species were available for the *MOCOS* 303 residue, and 94 species had either glutamic acid (n = 88) or aspartic acid (n = 6). These amino acids have similar properties: they are the only 2 amino acids with an acidic side chain. The 3 species that differed were the Mallard duck (alanine) and 2 fish (coelacanth and spotted gar; proline in both). Glycine, the variant present in the affected goat, is a neutral amino acid and was not the reference amino acid in any species.

We also assessed for interspecies variation at the *XDH* and *MOCOS* residues using variant sources available in Ensembl for humans and 5 nonhuman species (cow, horse, mouse, pig, and dog);[12,13] goat variant databases were evaluated separately as described below. No variants of any type were reported at the residues corresponding to caprine *XDH* 128 or *MOCOS* 303 for human, horse, mouse, pig, or dog. The cow had a synonymous variant reported at the *MOCOS* 303 residue but no missense variants. We next evaluated the position of all *XDH* variants (missense and synonymous) relative to locations demonstrated to alter enzyme function in experimental studies;[3] none were located at residues proven experimentally to be crucial for enzyme function. Similar data is not available for *MOCOS*.

To further assess the potential pathogenicity of all variants detected in the case goat, we determined their prevalence in other goats. The sire and dam were not available for testing, but blood was collected from healthy herd mates (n = 7, mixed breed goats) and livers were collected from goats submitted for necropsy for various causes (n = 12). Breeds for the necropsy submission goats included Boer (n = 4), Nubian (1), and mixed breed (7). Diagnoses included trauma, sepsis, pneumonia, mastitis, cardiac septal defect, and jejunal torsion; no goat had uroliths or a crystal nephropathy. These 2 groups, totaling 19 goats, were considered controls because of the absence of clinical signs and, in the case of the necropsy submission goats, lack of pathologic evidence of urinary tract disease. Genomic DNA was extracted and genotyped for the 17 variants to determine allele frequencies in the group of 19 control goats (Table 1). Primer sequences used for genotyping are provided in Supplementary Table 1. For some of the variants, genotyping failed for a subset of control goats; only those with clear sequencing results were included in allele frequency calculations. The *XDH* p.Leu128Pro variant was not found in any goat other than the case goat. The *MOCOS* p.Asp303Gly variant had a low allele frequency (0.05) in the herd mates and necropsy goats. Two control goats were heterozygous (1 herd mate and 1 necropsy goat), but no control goat was homozygous for the *MOCOS* p.Asp303Gly variant. In contrast, the other *XDH* and *MOCOS* variants were common (allele frequencies of 0.32-1.00).

The variant allele frequencies also were determined in goats available through the NextGen and VarGoats projects databases. The NextGen data (195 goats) was accessed through Ensembl, and the VarGoats data (248 goats) was acquired through a direct request to the VarGoats project. These projects combined contain whole-genome sequencing data from 443 goats from multiple continents. Phenotypes for these goats were not available. The databases were screened for the 17 *XDH* and *MOCOS* coding variants present in the case goat (Table 1). The *XDH* p.Leu128Pro variant was not present in either database, and 5 other variants were rare (allele frequency <0.05), including the *MOCOS* p.Asp303Gly variant. In the VarGoats database, 4 goats were called as homozygotes and 17 as heterozygotes for *MOCOS* p.Asp303Gly; country of origin was not reported for these samples. Further inspection of reads indicated that 1 of the goats originally called a homozygote was heterozygous for the variant (calls for both the reference and variant allele were present). Thus, the corrected *MOCOS* p.Asp303Gly counts in the VarGoats database were 3 homozygotes and 18 heterozygotes. This still may be an overestimation, because the call for 2 of the 3 homozygotes was based on a low number of reads (n = 4 and 6), and variant calls were not confirmed with targeted sequencing. In the NextGen database, there were no homozygotes but 6 goats (3 from Morocco, 2 from Iran, and 1 from Italy) were heterozygous for the variant. Overall, across the full study population of 462 goats (19 controls and 443 database samples), the *MOCOS* p.Asp303Gly allele frequency was 0.03 (32/924) and the frequency of homozygotes was 0.006 (3 of 462).

2 | DISCUSSION

Xanthine is a by-product of the purine degradation pathway. In this pathway, hypoxanthine and xanthine are metabolized to uric acid. This reaction is catalyzed by xanthine dehydrogenase (XDH). Molybdenum cofactor sulfurase (MOCOS) is necessary for XDH activity; it transfers sulfur to the molybdenum cofactor of XDH. Loss of function of either enzyme results in increased urine concentrations of xanthine (xanthinuria).[3] Causes for xanthinuria include drugs that inhibit XDH, leading to iatrogenic xanthinuria, or an inborn metabolic disorder, resulting in hereditary xanthinuria.[2–4] Hereditary xanthinuria is classified into subtypes based on the gene harboring the mutation; mutations within *XDH* result in xanthinuria type I (OMIM #278330) and mutations in *MOCOS* result in xanthinuria type II (OMIM #603592). These 2 subtypes of xanthinuria are clinically indistinguishable.[3]

Xanthine urolithiasis is rare in domestic species and in humans.[4,14] Iatrogenic xanthine uroliths have been reported in dogs treated with

allopurinol, an XDH inhibitor.[4] Xanthinuria also is reported to occur in sheep in association with a nutritional deficiency. Specifically, a study on sheep with xanthine calculi concluded that low dietary molybdenum could be causative because of molybdenum's role in purine metabolism.[15] Hereditary xanthinuria has been reported in cats (OMIA 001283-9685),[16–19] dogs (OMIA 001283-9615),[20–26] and cattle (OMIA 001819-9913).[27–29] In some reports, the genetic basis was established by sequencing;[26,27,29] in other cases, a primary cause was presumed after eliminating a history of XDH inhibitor use.[16–25,28] Similar to the goat in our study, many of the other domestic species with hereditary xanthinuria had severe disease characterized by a juvenile or young adult onset, nephrolithiasis, and renal pathology.[18–29]

Urolithiasis is frequently observed in goats and often associated with diet. The most common urolith types in goats are calcium carbonate, magnesium calcium phosphate carbonate, silica, and struvite.[30,31] Of 526 caprine uroliths analyzed by the Minnesota Urolith Center during a 27-year time period, only 1 had a purine composition.[31] The type of purine was not reported in the article, but personal communication with the Minnesota Urolith Center confirmed that this sample was a xanthine urolith from a pygmy goat. Although xanthine uroliths rarely are reported, they could be underdiagnosed in the goat population if advanced diagnostic testing or necropsy is not pursued.

The goat in our study was determined to have 2 putative disease-causing variants. The heterozygous *XDH* p.Leu128Pro variant was predicted to be deleterious with high confidence by multiple pathogenicity predictors. This variant was absent from 462 other goats screened. Hereditary xanthinuria is considered a recessive disorder, and, to our knowledge, xanthine urolithiasis has been reported only in patients that are homozygotes or compound heterozygotes for pathogenic variants in *XDH* or *MOCOS*. However, a 50% decrease in XDH activity and increased urinary xanthine excretion have been reported in obligate heterozygotes.[32] In our goat, the *XDH* p.Leu128Pro variant could be causal if a second pathogenic *XDH* variant is present that was not discovered by the sequencing approach (eg, a variant residing within a noncoding regulatory region) or if XDH activity is further decreased by the presence of the homozygous *MOCOS* p.Asp303Gly variant. We also cannot exclude the possibility that a partial decrease in XDH activity is sufficient to increase risk for xanthine urolithiasis in goats; species differences may exist that impact this risk. Appropriate samples were not available to analyze the goat for defects in RNA processing, gene expression, or XDH activity.

The homozygous *MOCOS* p.Asp303Gly variant is located in the aminotransferase class V domain of MOCOS and also was predicted to disturb enzyme function, but with lower confidence than the *XDH* \variant. The *MOCOS* p.Asp303Gly variant was present at low frequency in other goats. Of the 462 goats screened, 3 were found to be homozygous for the variant and 25 were carriers. Country of origin was reported for the NextGen goats, and carriers were present in samples from Morocco, Iran, and Italy, supporting an ancient origin of the variant in goats. The discovery of *MOCOS* p.Asp303Gly homozygous goats without known urinary tract disease could be explained by decreased penetrance of the mutation for clinical disease. Up to two-thirds of humans with hereditary xanthinuria are asymptomatic; clinical signs are observed only if urolithiasis or a crystal nephropathy develops.[33–35]

In conclusion, we report a case of xanthine urolithiasis and severe crystal nephropathy in a goat. Based on the absence of historical xanthine oxidase inhibitor treatment, the goat was presumed to have hereditary xanthinuria. Two putative pathogenic variants were discovered: a heterozygous *XDH* p.Leu128Pro variant and a homozygous *MOCOS* p.Asp303Gly variant. Both variants are considered possible causes of hereditary xanthinuria in this goat. Functional assays were not performed to confirm the variant effects, and a definitive conclusion as to the causal variant(s) could not be reached with the present data. Genotyping for the *XDH* p.Leu128Pro and *MOCOS* p.Asp303Gly variants and assessment for other variants in *XDH* and *MOCOS* should be considered if additional goats are diagnosed with xanthine urolithiasis in the future.

ACKNOWLEDGMENTS

We gratefully acknowledge the Minnesota Urolith Center for nephrolith identification, and the Texas A&M University VTPB histopathology laboratory for technical expertise. We thank Gwenola Tosser-Klopp, the leader of the VarGoats project, and the other VarGoats contributors for sharing variant calls for *XDH* and *MOCOS*. Partial support for EF was provided by an NIH ORIP K01 Mentored Research Scientist Development Award (K01-OD019912).

This work was presented as a poster at the 2017 annual meeting of the American College of Veterinary Pathologists.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Texas A&M University IACUC granted approval for collection of blood from goats. No other approval was required.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Vail KJ, Tate NM, Likavec T, et al. Hereditary xanthinuria in a goat. *J Vet Intern Med*. 2019;33: 1009–1014. https://doi.org/10.1111/jvim.15431