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## Summary

## Zusammenfassung

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## Clinical and biochemical signs in Fleckvieh cattle with genetically confirmed Fanconi-Bickel syndrome (cattle homozygous for Fleckvieh haplotype 2)

### *Klinische und biochemische Kennzeichen von Fleckvieh-rindern mit genetisch bestätigtem Fanconi-Bickel-Syndrom (Rinder homozygot für den Fleckvieh Haplotyp 2)*

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Fanconi-Bickel Syndrome (FBS) is an autosomal recessive disorder of the carbohydrate metabolism, which has been reported in human and some animals (OMIA 000366-9913). In Fleckvieh cattle it is caused by mutations in SLC2A2, a gene encoding for glucose transporter protein 2 (GLUT2), which is primarily expressed in liver, kidney, pancreas and intestines. The causal mutation resides in a previously reported Fleckvieh Haplotype 2 (FH-2). FH-2 homozygous individuals are rare, but due to widespread use of heterozygous bulls in artificial insemination, heterozygous animals are likely to be present in a larger number in the cattle population. Two clinical cases of Fleckvieh cattle with a syndrome resembling the phenotypic appearance of FBS are presented in the present study describing the association between the clinical manifestations of FBS and the postulated frameshift mutation in bovine SLC2A2. Clinical examination showed poor growth, retarded development, polyuria, and polydipsia. Laboratory analyses showed an increased plasma glucose but normal insulin concentration and increased renal glucose excretion. Histopathological examination of kidney and liver samples revealed massively increased liver glycogen storage and nephrosis. Sires of both cases were tested positive for being heterozygous carriers for the same frameshift mutation in SLC2A2 as was originally reported in Fleckvieh cattle. DNA of both cases described was analyzed and Sanger sequencing confirmed homozygosity for the frameshift mutation in SLC2A2.

**Keywords:** Glycogen storage disease, GLUT2, SLC2A2, haplotype, FH2

Das Fanconi-Bickel-Syndrom (FBS) ist ein autosomal rezessiver Defekt des Kohlenhydratstoffwechsels, der beim Menschen und einigen Tierarten nachgewiesen werden konnte. Bei Fleckviehrindern wird das FBS durch eine Mutation in SLC2A2, einem Gen das für den Glukosetransporter 2 (GLUT2) kodiert, verursacht. GLUT2 wird hauptsächlich in Leber, Niere, Pankreas und Darm exprimiert. Die kausale Mutation resultiert im bereits beschriebenen Fleckvieh Haplotyp 2 (FH-2), von dem homozygote Tiere in der Fleckviehpopulation selten sind, jedoch ist durch den weitverbreiteten Einsatz der künstlichen Besamung eine weite Verbreitung von heterozygoten Tieren sehr wahrscheinlich. Zwei klinische Fälle bei männlichen Fleckviehrindern, welche die phänotypische Ausprägung des FBS zeigten, werden in dieser Studie vorgestellt, um die Assoziation zwischen den klinischen Symptomen und der postulierten Frameshift Mutation im bovinem SLC2A2 zu zeigen. Die klinische Untersuchung zeigte schwachen körperlichen Wuchs, zurückgebliebene Entwicklung, Polyurie und Polydipsie. Die Laboruntersuchungen zeigten erhöhte Plasmaglukosekonzentrationen bei physiologischen Insulinwerten und Glukosurie. In der pathohistologischen

Untersuchung konnte eine massiv erhöhte Glukosespeicherung in der Leber und eine interstitielle Nephritis gezeigt werden. Die Väter beider vorgestellter Tiere wurden als heterozygote Träger und die zwei vorgestellten Tiere als homozygot für die Frameshift Mutation in SLC2A2 durch Sanger Sequenzierung bestätigt.

**Schlüsselwörter:** Glykogenspeicherkrankheit, GLUT2, SLC2A2, Haplotype, FH2

## Introduction

Due to a widespread use of a small number of key ancestors in artificial insemination in cattle breeding the effective population size is dramatically decreasing (Jansen et al., 2013; Daetwyler et al., 2014). Harmful recessive alleles may rapidly gain in frequency in cattle breeding populations and manifest themselves in fatal phenotypes (Nicholas and Hobbs, 2014).

Since the implementation of genome-based prediction in cattle breeding populations, at least the male selection candidates are genotyped with dense genotyping arrays in order to obtain their genome-enhanced breeding values (Meuwissen et al., 2001). Large-scale genotyping data also allow for the mapping of trait-associated variants in genome-wide association studies and for the identification of genomic regions with homozygous haplotype deficiency which may result from deleterious recessive alleles (VanRaden et al., 2011; Pausch et al., 2015).

This paper describes two cases of Fleckvieh cattle being homozygous for the same frameshift mutation in SLC2A2 as it was identified in Fleckvieh by Pausch et al. (2015) and the clinical signs in homozygous animals. The second case has been part of the study by Pausch et al. (2015). Fanconi-Bickel Syndrome (FBS), a rare glycogen storage disease, first described in man (Santer et al., 2002a; 2002b), is now also found in animals, see OMIA 000366-9913 (OMIA, 2015).

Contrary to other glycogen thesaurismoses (storage diseases) FBS is not caused by enzyme defects of glycogenolysis, but by a defect of the monosaccharide transporter GLUT2 in the cell membranes (Santer et al., 1997). This rarely occurring autosomal recessive disorder is characterized by massive glycogen accumulation in liver and kidney. Fasting hypoglycaemia, postprandial hyperglycaemia and hypergalactosaemia resulting in a chronic dysfunction in proximal renal tubuli are typical features in FBS diseased individuals. The aim of this report is to evaluate whether the clinical signs are consistent with genetic diagnosis of FBS.

## Material and Methods

### Patients

The two male animals were patients of the clinic for ruminants (Vetmeduni Vienna). A pedigree analysis was performed for both animals. The sires of both cases were shown to be heterozygous carriers of the same frameshift mutation in SLC2A2 as reported in Fleckvieh cattle by Pausch et al. (2015).

Animal 1: A Fleckvieh bull (dual purpose breed) was first examined in 1994. This animal was described clinically and has been already published as case report by Deinhofer (1996) and Deinhofer and Weißenböck (1998). At that time FBS was suspected, but since no genetic analysis was performed the presumptive diagnosis could

not be verified. Medical records and tissue were available and were used for analysis in the present study.

Animal 2: A 15 month old Fleckvieh bull with a history of growth retardation was referred to the clinic for ruminants in 2013. It was identified as one of two animals homozygous for a chromosomal segment on BTA 1 showing a significant homozygosity deficit in a scan of 25.544 Fleckvieh animals (Pausch et al., 2015). The bull grew normally to the age of six months but during the following nine months it did not grow and increase body weight as it would have been expected. The animal appeared quite healthy and had not suffered from any infectious or non-infectious disease during this period and stayed at the clinic for 50 days for observation and diagnosis before it was euthanized.

### Clinical examination

Physical examination was performed on the day of arrival before specific diagnostic procedures were initiated. During the stay in the veterinary hospital the animal was clinically examined twice a day. The body weight of the animal was measured weekly using an electronic system. On several occasions the daily water intake was estimated using a water basin. Subsequently, urine of animal 2 was continuously sampled and the volume was measured over a period of 12 h, the volume per day was extrapolated. The liver was ultrasonographically examined and its dimensions determined as described by Braun (1997). Blood, rumen fluid and urine samples were taken for haematological and biochemical analysis and urine analysis from both patients.

### Laboratory work

All laboratory analyses were performed in the central laboratory of the Vetmeduni Vienna. The RBC and WBC were measured using an automatic haematology analyser (ADVIA 2120i, Siemens Healthcare, Vienna, Austria). The biochemical parameters: glucose, insulin, total protein, albumin, cholesterol, NEFA, total bilirubin, creatinine, potassium, sodium, AST, GLDH, and GGT were measured in plasma using an automatic analyser (Cobas 6000/c501, Roche Diagnostics GmbH, Rotkreuz Switzerland; Kodak Ektachem DT II system, Eastman Kodak company, Rochester, New York, US). The GGT activity and the concentrations of glucose, creatinine, potassium and sodium were measured in urine. The GGT/creatinine ratio and the glucose excretion were calculated. The fractional excretion (FE) of potassium (K) was calculated using following equation  $FE_K = (K_{urine} \times Crea_{blood}) / (K_{blood} \times Crea_{urine}) \times 100$ . The fractional excretion of chloride and sodium were calculated accordingly (Lefebvre et al., 2008).

### Genetic analysis

Animal 1: Paraffin embedded (1994) liver tissue from the archive of the Institute Pathology and Forensic Veterinary Medicine was transferred to the chair for animal breed-

ing of the Technische Universität München (Technical University Munich), Freising, Germany for further analyses.

Animal 2: Liver and kidney tissue from ultrasound guided biopsy and post mortal taken pancreas and intestine samples were used and transferred to the Technische Universität München for gene sequencing.

PCR primers ATGAGAAACGGTGCACATGA and GCAGCATCAATGCCACTAGA were designed according to Pausch et al. (2015) to genotype the rs379675307-variant in two animals with retarded growth using Sanger sequencing.

### Histology and histopathology

Tissue samples from animal 2 were taken from liver, kidneys, pancreas, mesenteric lymph node, intestine, heart, and lung. In addition, samples from liver and kidney were taken from a healthy control animal. Samples were fixed in 4% neutral buffered formaldehyde and embedded in paraffin. Sections (3 µm) were routinely stained with hematoxylin and eosin (HE); for glycogen detection, liver and kidney sections were additionally stained with Best's carmine (glycogen stain) and periodic acid-Schiff (PAS; staining kit, Morphisto, Germany). Consecutive sections were stained with PAS after digestion with diastase (PAS-D), an enzyme that breaks down glycogen, for 1h at 37°C.

## Results

### Clinical findings

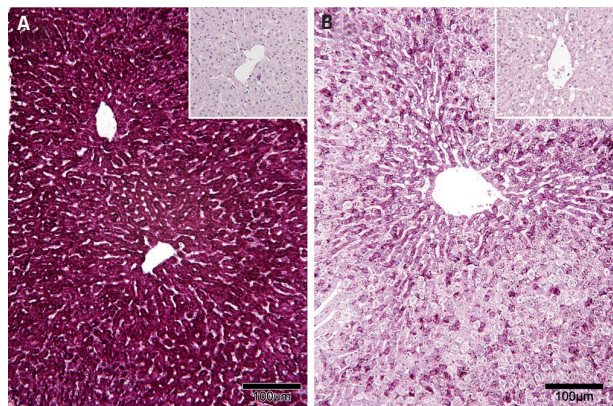
Animal 1: A nine month old Fleckvieh bull (160 kg) with a history of growth retardation was hospitalized in 1994. The animal was weak and severely emaciated, the decreased skin elasticity indicated dehydration, other clinical parameters turned out to be physiological, despite the presence of polyuria, polydipsia and glucosuria (Deinhofer, 1996). DNA of the animal was extracted from a Paraffin-embedded sample and Sanger sequencing confirmed homozygosity for the same frameshift mutation in SLC2A2 as reported by Pausch et al. (2015), that is supposed to result in a non-functional GLUT2.

Animal 2: The Fleckvieh bull was 15 months old, weighed 268.5 kg at admission. It was kept at a beef fattening farm. The bull gained 330 g per day on average while it was hospitalized 50 days at the clinic in 2013. Molecular-genetic analysis confirmed homozygosity for the same frameshift mutation in SLC2A2 that is supposed to result in a non-functional GLUT2 (Pausch et al., 2015).

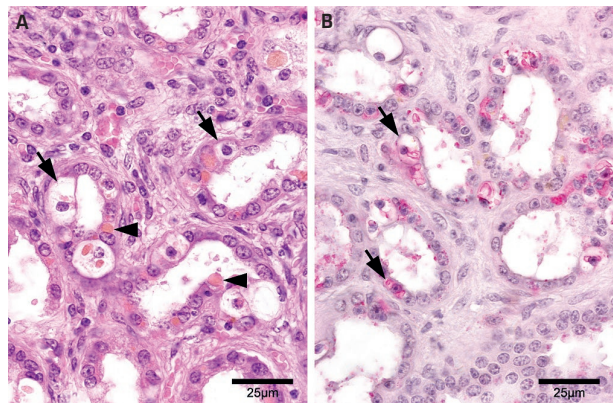
The animal was quiet but behaviourally normal. Postural abnormalities could not be assessed. The body condition was decreased; the bones protruded as a result of muscular wasting (Fig. 1). The body temperature, pulse and respiratory rates were within reference ranges. Hair coat appeared rough and several hairless patches were present. Skin turgor was slightly decreased, which can be linked to dehydration. The examination of the mucous membranes did not show any abnormal signs, the muzzle, nostrils, oral cavity, eyes and eyelids were moist, shiny, smooth and pale pink. Mandibular, parotid, medial retropharyngeal, superficial cervical and subiliac lymph nodes were flaccid, easily movable on the underlying tissue and not painful. The examination of circulation involving the heart, arteries, capillaries and veins failed to show any abnormality. A similar result was obtained



**FIGURE 1:** Stunted male Fleckvieh cattle with Fanconi-Bickel syndrome.



**FIGURE 2:** Micrograph of PAS stained liver from the Fanconi Bickel animal (A) and a control animal (B). PAS-D (inset) shows the positive diastase test.



**FIGURE 3:** Section of kidney in an area with mild interstitial nephritis. (A) Marked vacuolisation of several epithelial cells of distal tubules (arrows), with some of them showing brownish droplet-like inclusions (arrowheads); HE, x40. (B) Pinkish colouring of granular cytoplasmic structures in numerous epithelial cells of distal tubules (arrows); glycogen stain, x40.

with the clinical examination of the respiratory system (respiratory rate, type of breathing, awareness of audible stenosis sounds, coughs, air flow from both nostrils). Respiratory rate was 20 per minute, breathing type was costo-abdominal and the caudal lung field border ended at the 10<sup>th</sup> intercostal space, the percussion could be



described as full lung sound with good resonance. Vesicular breathing could be heard over the whole lung field.

The bull had an increased water intake, while feed intake and rumination was normal. Examination of the digestive system from the oral cavity, pharynx via oesophagus to the forestomachs including adspsection of the left flank again showed no abnormalities with a well filled rumen, normal rumen layers and two contractions in 5 min.

The urine volume of the bull was 34 l in twelve hours, while the water intake was 36 l during that time period. Both water intake and urine volume were severely increased in comparison to the normal physiological volumes for a young bull.

### Ultrasonographic examination in animal 2

The liver parenchyma could be visualized from 12<sup>th</sup> to 7<sup>th</sup> intercostal space and appeared to have homogenous echogenicity. The liver size and position was measured, measurements are given in Table 1. The dimensions of the liver were enlarged for an animal of this weight (Tab. 1), resembling with reference measures of animals twice that weight (Braun, 1997). However, the bull had about 60% of the body weight of a normally developed animal. To compare the liver size in Fleckvieh bulls of the same body weight liver ultrasonography was performed and measurements were taken in eleven clinically healthy bulls since no reference values seem to be available in the literature (Tab. 1).

### Histological examination (animal 2)

Histology of the liver (Fig. 2) showed intense staining with PAS demonstrating glycogen accumulation compared to only discrete glycogen storage in the control animal. Figure 3 shows sections from kidney of the affected animal. Moderate glycogen accumulation in renal tubular cells was seen. No PAS positive reaction was seen in the kidney tissue of a healthy control animal.

### Fractional excretion, urine glucose and protein loss for animal 2

There were substantial losses of glucose and protein via the urine. The estimated loss of glucose varied between 494 and 798 g per day. The calculated urinary loss of protein was between 11.0 to 13.8 g per day (Tab. 2).

**TABLE 1:** Ultrasonographic visible liver extension (cm) FBS bull (268 kg) and reference bulls (n = 11, Fleckvieh, Finishing unit, BM = median 248 kg, SD: 31.22)

		12 <sup>th</sup> ICS	11 <sup>th</sup> ICS	10 <sup>th</sup> ICS	9 <sup>th</sup> ICS
Control animals	Mean	13.64	21.82	19.59	12.73
	standard deviation	5.39	3.48	2.83	5.06
FBS patient (animal 2)		14	32	25	22
Average difference of controls to FBS patient		<b>0.36</b>	<b>10.18</b>	<b>5.41</b>	<b>9.27</b>

Fractional excretion describes the percentage of electrolytes or minerals, which is filtrated in the glomerulus as part of the primary urine and finally is eliminated in the urine. The resorbed part is retained in blood circulation. The FCI for potassium was 140.2% (reference 35–100), for sodium 2.2% (0.01–0.45) and for chloride 3.7% (0.68–2.25) in this case (Lefebvre et al., 2008).

### Pathological examination

#### Animal 1

Pathological examination revealed emaciation with complete exhaustion of fat covering heart and kidneys. Severe liver cirrhosis with a huge amount of glycogen stored in the liver cells was diagnosed. The kidneys showed moderate glycogen nephrosis and pancreas appeared normal.

#### Animal 2

The Fleckvieh bull was euthanized and necropsy was performed. The animal was severely anaemic. The heart appeared normal apart from a slight hydropericardium. The lungs showed mild emphysema, and a slight peribronchitis. Pulmonary arteries revealed a moderate hypertrophy and hyalinization of tunica media. The liver (55 x 30 x 11–18 cm) was moderately fragile and showed a centrolobular dissociation of the liver cells, and discrete interstitial fibrosis with lymphocytic infiltrates. Furthermore, hepatocytes were severely swollen and the cytoplasm was cloudy, with fine granulation. Many hepatocytes had homogenous eosinophilic inclusion bodies, which, in contrast to the fine granular structures, remained negative

**TABLE 2:** Analysis of urine samples of the 2 patients

Parameter	Unit	Animal 1		Animal 2			Reference (adult cattle)
		day 1	day 42	day 1	day 7	day 25	
Colour		Light yellow	Light yellow	Light yellow	Light yellow		Light-dark yellow
Urine specific gravity	g/l	<b>1012</b>	<b>1006</b>	<b>1014</b>	<b>1011</b>		1020–1040 <sup>1</sup>
pH	value	7	5	7	7		7.0–8.4 <sup>1</sup>
Glucose	mmol/l	+++	+++	<b>65.05</b>	<b>40.35</b>		0 <sup>1</sup>
Calculated loss of glucose	g/day			<b>796.96</b>	<b>494.36</b>		
Protein	mg/l			<b>203</b>	<b>161</b>		0 <sup>1</sup>
Calculated loss of protein	g/day			<b>13.8</b>	<b>10.95</b>		
Creatinine	μmol/l			<b>2033.25</b>	<b>1069.66</b>		2200–7100 <sup>1</sup>
Protein:creatinine	ratio			0.88	1.33		0.5
FENa <sup>a</sup>	%					<b>2,23</b>	0.01–0.45 <sup>2</sup>
FECl <sup>b</sup>	%					<b>3,7</b>	0.68–2.25 <sup>2</sup>
FEK <sup>c</sup>	%					<b>140.19</b>	35–100 <sup>2</sup>

aFENa: fractional excretion of sodium

bFECl: fractional excretion of chloride

cFEK: fractional excretion of potassium

Values outside the physiological reference ranges are indicated in bold type. Physiological values were obtained based on following references:

<sup>1</sup>Fürll M (2014)

<sup>2</sup>Lefebvre et al. (2008)

**TABLE 3:** Analysis of blood samples of the 2 patients

Parameter	Unit	Animal 1: day 1	Animal 2: day 1	Reference (adult cattle)
Glucose	mmol/l	<b>3.7</b>	<b>4.2</b>	2.2–3.3 <sup>1</sup>
Creatinine	μmol/l	91	97.24	88–177 <sup>1</sup>
Total protein	g/l		68	60–80 <sup>1</sup>
Albumin	g/l		35	30–42 <sup>1</sup>
AST	μkat/l		<b>1.36</b>	< 1.34 <sup>1</sup>
GLDH	μkat/l		<b>2.64</b>	< 0.50 <sup>1</sup>
GGT	μkat/l		<b>1.73</b>	< 0.834 <sup>1</sup>
Bilirubin (total)	μmol/l		2.22	< 5.00 <sup>1</sup>
Cholesterol	mmol/l		4.22	> 2.00 <sup>1</sup>
NEFA	mmol/l		0.19	0.4 <sup>2</sup>
Insulin	pmol/l	58.4	71.8	57.72–101 <sup>3</sup>

Values outside the physiological reference ranges are indicated in bold type.

Physiological values were obtained based on following references:

<sup>1</sup>Fürll (2014)

<sup>2</sup>Oetzel (2004)

<sup>3</sup>Blum et al. (1981)

with PAS and glycogen stain. The kidneys were patchy inhomogeneous and also fragile. A moderate interstitial nephritis was seen with severe swelling of the epithelia of the tubules with an empty or cloudy-granular structured cytoplasm (Fig. 3). In some of the tubular epithelia brown, droplet-like inclusions were seen, which could not be stained in PAS and glycogen staining, again in contrast to the granular cytoplasmic structures (Fig 3). The mesenteric lymph nodes were severely swollen, due to follicular hyperplasia. The intestine revealed severe eosinophilic enteritis with numerous obstructed and dilated crypts and massively enlarged intramural lymph follicles. The spleen was follicular hyperplastic, pancreas and fore stomachs showed no abnormalities.

## Discussion

The present study describes the first full clinical laboratory and genetic characterization of a syndrome resembling the clinical and pathological signs of FBS in two Fleckvieh bulls caused by frameshift mutation in SLC2A2. The fact that both cases presented in this report were male was coincidence; to the authors opinion the gender of the animals is not affecting the described symptoms.

Both bulls were stunted for their age. The body weights were far too low for their ages, an average Fleckvieh bull should have a body weight of approximately 450 kg at an age of one year and should have a daily weight gain of 1175 g per day on average during the final fattening period (ZuchtData, 2014) until being slaughtered at the age of 17 to 20 months at a body weight of 700 to 800 kg. Differential diagnoses for stunted animals generally include chronic disease, mainly affecting respiratory and gastro intestinal tract (Gifford et al., 2012). Besides that endoparasitism is a common cause for growth retardation in cattle (Corwin, 1997). Polyuria and Polydipsia is described in FBS affected individuals (Moe et al., 2009), which could also be shown in these cases. The second patient's urine volume was about five to 14 times the reference volume, reference range for urine volume in cattle is 17–45 ml/kg body weight/d (Fürll, 2014). The bulls water intake was three to four times greater than

the amount beef cattle at this bodyweight would need (between 18 and 30 l per day depending on the outdoor temperature) (Meyer et al., 2006; Brew et al., 2011).

Fractional excretion (FE) tests are used to determine renal dysfunction in patients with kidney diseases, among these Fanconi's syndrome (Lefebvre et al., 2008). In this case the bull showed renal reabsorption defects leading to excessive urinary loss of water, sodium, potassium and chloride. Although the defective GLUT2 resulted in massive glycogen accumulation in the liver, most glucose was excreted in the urine. Glucose loss with the urine is described in chronic kidney failure, which can be caused by severe kidney damage or hormonal or receptors' dysfunction, seen in diabetes mellitus type 2 (Taniyama et al., 1995).

The increased size of the liver, caused by glycogen storage, is a characteristic sign of FBS in affected individuals (Santer et al., 1998). Although to our best knowledge there are no reference ranges available for the size of the liver for animals of this age group; compared to reference values for adult cattle (Braun, 1990) the size of the liver of the bull in the present study was increased since it was within the reference ranges of animals twice as heavy and was significantly enlarged compared to the size of bulls' livers in our control group (Tab. 1). Enlarged liver sizes are known in cattle due to fatty liver syndrome, which could be ruled out in both cases by histological and blood enzyme examinations.

Santer et al. (1998) published a case report of FBS in man. The patient's short stature, protuberant abdomen, hyperlordosis and excessive hepatomegaly were documented at the ages of eight months, 2.8 and 3.8 years. Histological examination of the liver tissue showed severe steatosis and storage of glycogen. Renal dysfunction in form of a tubular nephropathy was clinically diagnosed due to excessive glucosuria, moderate hyperphosphaturia and the presence of a hypophosphataemia and proteinuria. Hypoglycaemia and ketonuria in fasting and hyperglycaemia in the post absorptive state was also described as was increased sensitivity to insulin. When the patient was 52 years old, he was 140 cm in height and weighted 43 kg. He had never had continuous medication after the first hospitalization in childhood. Laboratory data from blood and urine samples showed characteristic results for FBS. These clinical and laboratory findings are similar to FBS in Fleckvieh cattle as shown in the present study as well (Tab. 3).

In the present case glycogen storage was confirmed by PAS staining of the liver biopsy. The morphological changes of the hepatocytes and tubular epithelia, the moderate glycogen storage, fibrosis of the liver and anaemia, which are related to the cluster of symptoms have also been described in Fanconi-Bickel.

In conclusion, FBS should be a differential diagnosis in cases of Fleckvieh cattle showing severe growth retardation, polyuria, glucosuria and polydipsia. The clinical findings, necropsy and laboratory data here strongly support the diagnosis of FBS.

Breeders can avoid risk matings, because all Fleckvieh bulls used in artificial insemination are tested for the described frameshift mutation in SLC2A2. If breeders want to use a known FH2 carrier they should ensure that those are only mated to cows homozygous for the normal allele. If heterozygous carriers of the frameshift mutation are present in the pedigree of animals with the above mentioned signs, genetic testing is recommended (ZAR, personal communication).

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## Conflict of interest

All authors declare that they have no conflict of interest regarding the present study and manuscript. The study was financed by institutional funds, no external funding was used.

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