First European case of recessive *early-onset muscle weakness* syndrome in a Holstein calf

B. A. Weber[1], E. E. Akyurek[2], F. R. Seefried[3], R. Sacchetto[2], C. Drögemüller[1], J. P. G. Jacinto[1,4]

[1]Institute of Genetics, Vetsuisse Faculty, University of Bern, Switzerland; [2]Department of Comparative Biomedicine and Food Science, University of Padova, Italy; [3]Qualitas AG, Zug, Switzerland; [4] Clinic for Ruminants, Vetsuisse Faculty, University of Bern, Switzerland.

https://doi.org/10.17236/sat00481

Eingereicht: 13.12.2025
Angenommen: 23.04.2026

Erster europäischer Fall mit rezessivem *Early-onset Muscle Weakness* Syndrom bei einem Holstein-Kalb

Das *Early-onset Muscle Weakness* Syndrom (MW) ist eine 2022 erstmalig in den USA beschriebene genetische Erkrankung bei Holstein-Rindern, die durch eine rezessiv vererbte Variante im *CACNA1S*-Gen verursacht wird. Dieser Bericht dokumentiert den ersten bestätigten MW-Fall beim Holstein-Rind in Europa. Ein 17 Tage altes weibliches Schweizer Holstein-Kalb wurde wegen fortschreitender Schwäche und der Unfähigkeit, ohne Hilfe aufzustehen, vorgestellt. Bei der klinischen Untersuchung wurden eine generalisierte Muskelatrophie und ein Tremor, eine breite Standhaltung sowie die Unfähigkeit, ohne Hilfe eine stehende Haltung einzunehmen, festgestellt. Die hämatologischen und biochemischen Untersuchungen waren unauffällig, mit Ausnahme einer leichten Monozytopenie und eines reduzierten Plasmakreatininspiegels. Die histopathologische Untersuchung der Muskeln *Mm. semitendinosus* und *semimembranosus* zeigte eine ausgeprägte Variabilität der Fasergrösse, abgerundete, hypertrophe Fasern, kleine Fasern mit zentralen Kernen, eine leichte mononukleäre Infiltration sowie vermehrtes Bindegewebe. Diese Befunde, stimmen mit einer chronischen myopathischen Veränderung überein. Gemäss der Stammbaumanalyse war das betroffene Kalb ingezüchtet und konnte auf zwei bekannte US-amerikanische MW-Anlageträger zurückgeführt werden, was auf eine rezessive Vererbung hindeutete. Die genetische Untersuchung bestätigte die *CACNA1S*-Homozygotie beim Fall und eine Heterozygotie der beiden Elternteile. Die Frequenz dieses Defektallels liegt in der Schweizer Holstein-Population bei 0,56 % und 1,07 % beim Swiss Fleckvieh. MW sollte als Differentialdiagnose bei jungen Kälbern dieser beiden Rassen, die Festliegen und Schwächeerscheinungen zeigen, in Betracht gezogen und entsprechend mittels genetischer Diagnostik getestet werden.

Schlüsselwörter: *Early-onset muscle weakness*, Erbfehler, Festliegen, Rind, rezessiver Gendefekt, Zucht

Abstract

Early-onset muscle weakness (MW) syndrome is a genetic disorder in Holstein cattle, that was first described in the US in 2022 and is caused by a recessively inherited variant in the *CACNA1S* gene. This report documents the first confirmed case of MW in Holstein cattle in Europe. A 17-day-old female Swiss Holstein calf was presented for progressive, non-ambulatory weakness and inability to stand up without assistance. Clinical examination revealed generalized muscle atrophy and tremors, a wide-based stance, and inability to acquire the quadrupedal stance without assistance. Hematologic and biochemical analyses were unremarkable, except for mild monocytopenia and reduced plasma creatinine. Histopathological analysis of semitendinosus and semimembranosus muscles revealed pronounced fiber size variability, rounded hypertrophic fibers, small fibers with central nuclei, mild mononuclear infiltration, and increased connective tissue, findings consistent with chronic myopathic change. Pedigree analysis revealed that the affected calf was inbred and could be traced back to two known US MW carriers suggesting recessive inheritance. Genetic testing of the case confirmed homozygosity for *CACNA1S*, whereas both parents were heterozygous. The estimate of the frequency of this defect allele in the Swiss Holstein population is 0,56 %and 1,07 % in Swiss Fleckvieh. MW should be considered as a differential diagnosis in young calves of these two breeds presenting with signs of recumbency and weakness and should be tested accordingly using genetic diagnostics.

Keywords: *cattle, genetic defect, rearing loss, recessive disorder, recumbency, selection*

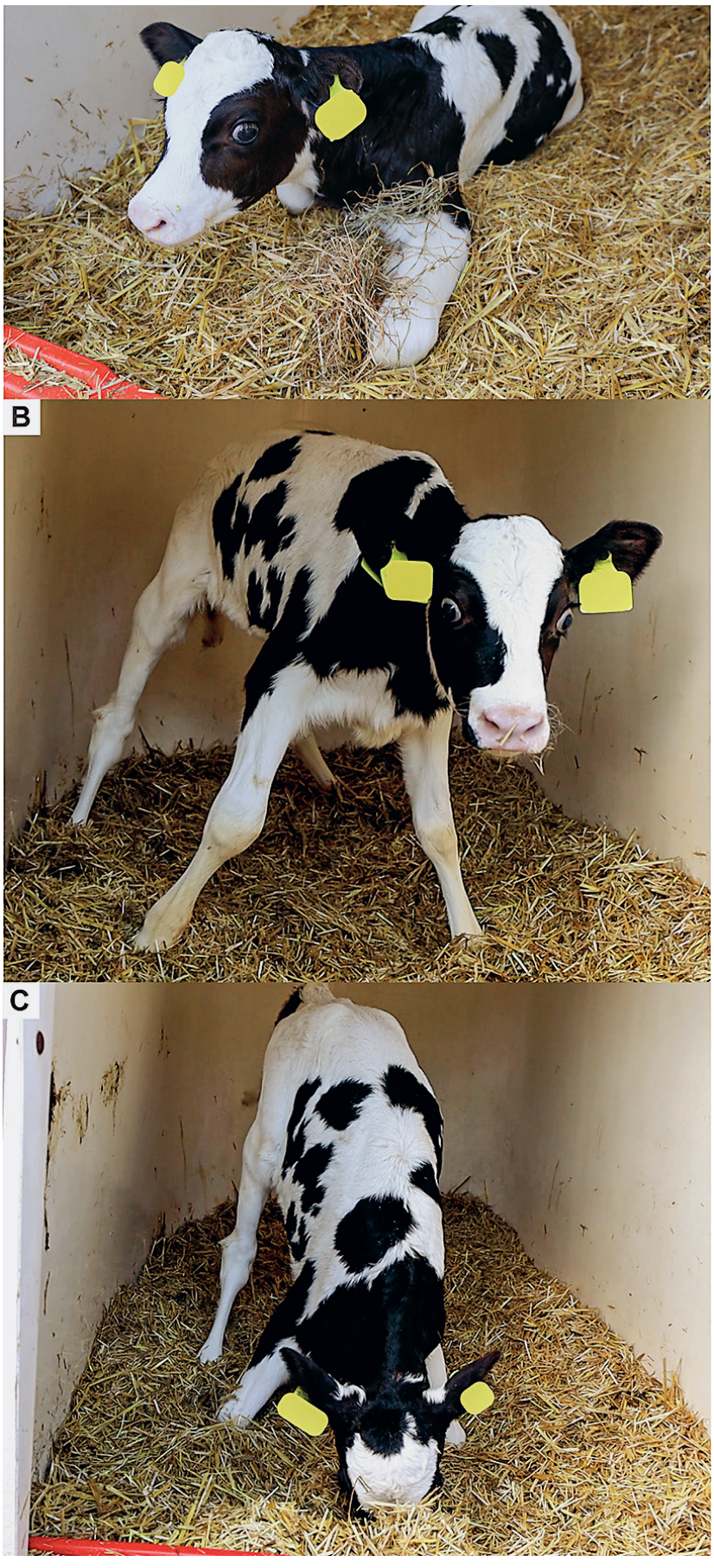

Figure 1: Clinical presentation of early-onset muscle weakness syndrome in a 17-day-old female Swiss Holstein calf. A) Calf in sternal recumbency. B) Quadrupedal stance, achieved with assistance, showing a wide-based stance and uneven weight distribution. C) After a few minutes in quadrupedal stance the calf flexed the thoracic limbs and is not able to extend the limbs to acquire the quadrupedal stance without assistance.

Introduction

In Holstein (HO) cattle, several recessively inherited disorders have been identified in the literature, including retinitis pigmentosa (RP), bovine lymphocyte intestinal retention defect (BLIRD / LR), thrombopathia (TP), bovine dilated cardiomyopathy (CMP), cholesterol deficiency (CD), bovine leukocyte adhesion deficiency (BLAD), brachyspina (BY), complex vertebral malformation (CVM) and early-onset muscle weakness (MW) syndrome.[8,13] As a result of sustained and targeted selective breeding efforts, the incidence of several disorders, such as BLAD and TP, has been substantially reduced also in the Swiss HO population, and they are now considered of negligible importance for the breed.[12,17] To date, no cases of MW have been documented in any European country. Previously, the disorder had only been reported in HO calves in the USA, Japan, and Australia.[3,5,6,10]

Bovine MW is a neuromuscular disorder first described in 2022 in the US HO cattle population, where it was characterized by generalized muscle weakness.[6] The condition is caused by a recessively inherited pathogenic variant in the *CACNA1S* gene (OMIA:002819-9913), first identified in 2024, although tracing back the haplotype revealed a key ancestor HO sire named *Southwind Bell of Bar-Lee* born in 1984.[3] The *CACNA1S* gene encodes the α1s subunit of the dihydropyridine receptor (DHPR), a component of the voltage-dependent L-type calcium channel (Cav1.1) highly expressed in skeletal muscle.[16] To date, this genetic disorder has only been reported in the HO breed and was initially reported as "recumbency", which exhibits a congenital onset with a high mortality rate exceeding 50 % before six weeks of age.[3,6] Affected calves homozygous for the *CACNA1S* variant typically present with muscle weakness and an inability to quadrupedal stand without assistance, however the severity, recovery, and recurrence of clinical signs vary among individuals.[3,6] These variable outcomes have led to the hypothesis of incomplete penetrance.[3] Neurological clinical examination, cerebrospinal fluid and intracranial pressure are reported to be unremarkable.[6,10] Complete blood count (CBC) and plasma biochemistry analysis of affected calves are reported to show no major abnormalities.[6,10] Furthermore, no significant gross or histopathological abnormalities in skeletal muscle have been reported to date.[6,10]

The aim of the present case report was to (1) describe the clinicopathological phenotype of the first HO calf affected by MW in Europe, and (2) estimate the allele frequency of the causal variant in the Swiss dairy cattle population.

Case report

The here described case was a female HO calf affected by sternal recumbency since birth. The calf was a result of arti-

ficial insemination with semen of a purebred HO sire on a HO dam. Both parents were reported to be healthy. The birth was an eutocia and the calf received 3 liters of colostrum immediately postpartum. The owner reported that it had a good appetite and did not exhibit coughing or diarrhea.

During the first week of life, the calf was only able to acquire a quadrupedal stance with assistance. Once in the position, it remained standing for approximately 10 minutes without assistance, but the duration of standing progressively decreased thereafter.

At 17 days of age, the calf was referred to the Institute of Genetics at the University of Bern due to persistent recumbency. A complete clinical examination was performed. The calf showed a normal mental status, tachypnoea (60 breaths/ minute), tachycardia (152 beats/ minute), and the rectal temperature was within normal limits (39,1°C). The nutritional status was good. Additionally, a slight exophthalmos was noticed.

The calf was presented in a physiological sternal recumbency with the head held upright and aligned with the spinal axis (Figure 1A). The animal did not attempt to adopt a quadrupedal stance, even when stimulated, but it was able to reposition itself from lateral to sternal recumbency and could move its limbs voluntarily. Marked muscle atrophy was noticed in all limbs, most prominently in the pelvic limbs. When placed in a quadrupedal stance, the calf was able to maintain the stance unassisted for approximately 30 seconds to a few minutes before collapsing and returning to sternal recumbency. It exhibited a wide-based stance of all four limbs, kyphosis, and uneven weight distribution (Figure 1B). After several seconds, visible muscle tremors developed, particularly in the thoracic limbs. The calf made minimal attempts to reposition its limbs and often failed to do so even when losing balance. It occasionally attempted to make a few steps, mainly with the pelvic limbs, which resulted in collapse of the thoracic limbs (Figure 1C; Video 1). Additionally, neurological examination revealed a reduced menace response, ear reflex, torso sensitivity, and panniculus reflex bilaterally. Proprioceptive deficits were also present. The flexor reflexes in all four limbs were normal. All other findings on clinical examination were unremarkable.

Blood samples from the calf were collected for a CBC, plasma biochemistry, and genetic testing. Additionally, an EDTA-blood sample from the dam and a semen sample of the sire were obtained for genetic testing. The examination and sampling were conducted with the owner's consent and under authorization from the Cantonal Committee for Animal Experiments (Canton of Bern; permit BE94/2022).

The CBC revealed monocytopenia ($0{,}33 \times 10^9$/L; reference values: $0{,}92 – 1{,}26 \times 10^9$/L) and plasma biochemistry showed reduced creatinine (43 µmol/L; reference values: 62,3 – 133,0 µmol/L). The remaining parameters were within normal range (Supplementary Table S1).

Based on the clinical presentation and pedigree analysis, the *CACNA1S*-related MW was considered a plausible differential diagnosis. For the genetic testing, genomic desoxyribonucleic acid (DNA) was isolated from EDTA-blood of the calf and the dam, and from semen of the sire. The DNA was extracted using the Promega Maxwell RSC DNA System (Promega, Dübendorf, Switzerland). Then genotyping by PCR and Sanger sequencing was performed, as previously reported.[3] The results identified the calf as *CACNA1S* homozygous mutant, and the dam and sire as heterozygous (carriers).

A follow-up with the owner at 24 days of age revealed marked clinical deterioration (Video 1) . Despite the owner's extensive care, including supportive bedding and physiotherapy. The calf was no longer able to stand, even with assistance, required feeding while recumbent, and showed reduced appetite with intermittent loss of the suck reflex. Given the progressive weakness and confirmed homozygosity for the *CACNA1S* variant, the calf was euthanized.

The video shows the clinical detoriation of a Holstein calf with CACNAIS-related early-onset muscle weakness (MW) syndrome.

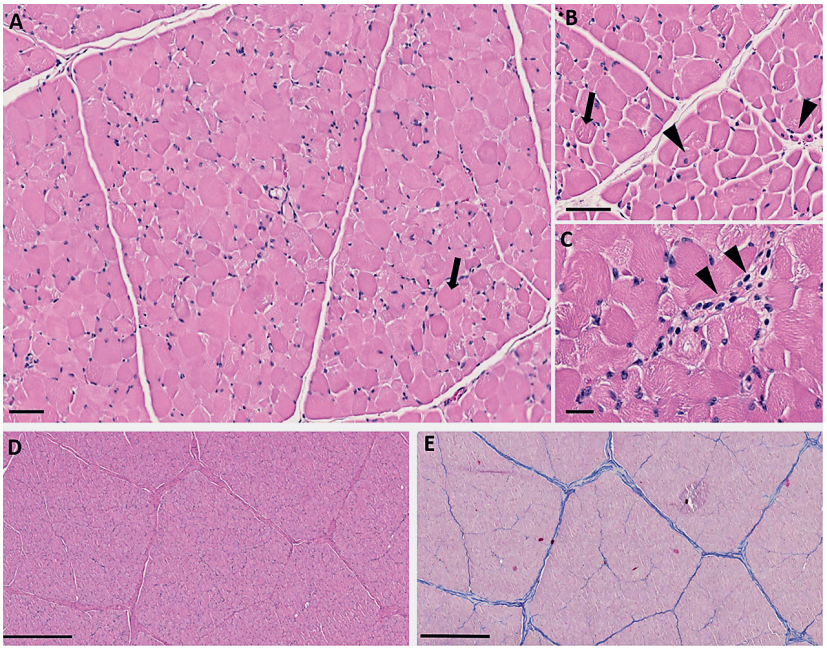

Figure 2: Histological features of skeletal muscle sections from the MW-affected female Swiss Holstein calf. Transversal sections from *M. semimembranosus* (A, B, C) and *M. semitendinosus* (D, E) muscles stained with Hematoxylin and Eosin (H&E) (panels A, B, C, D) or Azan–Mallory (panel E) methods. Scale bar: 50 µm panels A, B; 20 µm panel C and 500 µm panels D, E. In the histological staining atrophic round shaped fibers non-centrally-nucleated (2A – black arrow), densely stained fibers with fragmented sarcoplasm (2B-black arrow), regenerating small rounded myofibers with centrally located nuclei (2B – black arrowhead) and inflammatory mononuclear cells (C – white arrowheads) can be observed.

Two postmortem muscle biopsies were collected from *M. semitendinosus* and *M. semimembranosus* of the right pelvic limb. Both muscle samples were fixed in 10 % buffered neutral paraformaldehyde, washed in phosphate-buffered saline and dehydrated through a graded series of ethanol. Samples embedded in paraffin were cut at 5 µm and stained with Hematoxylin and Eosin (H&E) and Azan–Mallory. Images were acquired by the automated slide scanner (Axioscan 7, Carl Zeiss Microscopy, GmbH, Jena, Germany).

Routine morphological (H&E) analysis was used for histopathological evaluation of the skeletal muscle biopsy sections (Figure 2). A substantial heterogeneity in myofiber size distribution was observed. Groups of large darker, round shaped fibers non-centrally nucleated or densely stained fibers with fragmented sarcoplasm were intermingled with usual polygonal shape fibers. Conversely, clusters of small rounded myofibers exhibiting centrally located nuclei, could be observed. Moreover, mild inflammatory mononuclear cell infiltration was present. The presence of connective tissue was determined using Azan–Mallory staining. An increased amount of connective tissue was observed in the epimysium and perimysium of both the *M. semitendinosus* and the *M. semimembranosus* muscles.

In 2019/2020, when the pathogenicity of the *CACNA1S* variant was still unknown, a large custom DNA marker array was used in the routine genotyping workflow for Swiss cattle breeding. This custom array contained more than 310,000 markers, including the *CACNA1S* variant, which is now known to cause MW. Based on this data, the allelic frequency of the *CACNA1S* variant could be estimated at 0,56 % in the Swiss HO and 1,07 % in the Swiss Fleckvieh (SF) population (Table 1). The variant is absent in all other breeds, including the Original Simmental population. No deviation from Hardy-Weinberg equilibrium was observed.

A pedigree analysis of the MW-affected calf revealed several inbreeding loops (Figure 3). The calf was inbred to two previously reported MW carrier HO bulls.[3] *Seagull-Bay Supersire*, born in 2010 (3rd and 6th generation), and his sire *Roylane Socra Robust*, born in 2008 (5th and 7th generation).

Table 1: Occurrence of the MW causing recessive allele in Swiss dairy cattle genotyped in 2019/20.

Population	Total	MWF	MWC	MWS	AF (%)
Holstein (HO)	10935	10812	123	0	0,56
Swiss Fleckvieh (SF)	1725	1688	37	0	1,07

Abbreviations: MWF = homozygous normal, MWC = heterozygous carrier, MWS = homozygous affected, AF = allele frequency.

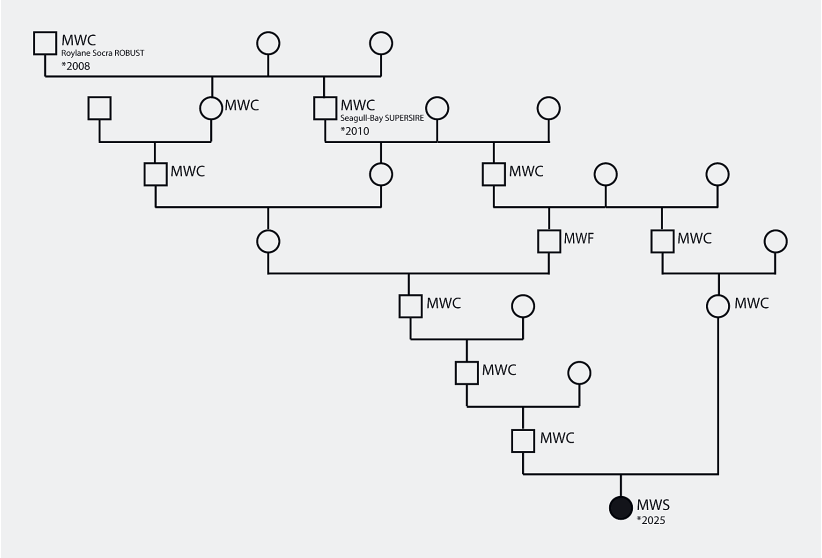

Figure 3: Pedigree of the inbred MW-affected female Swiss Holstein calf. Note that the pedigree shows several loops of inbreeding. Females are represented by circles and males by squares. The MWS-affected animal born in 2025 was tested as a homozygous carrier of the causal CACNA1S variant and is represented as case by a black-filled symbol. Both parents were confirmed to be heterozygous carriers (MWC). The MW genotypes of all ancestors with known status are shown as homozygous free non-carriers (MWF) or heterozygous carriers (MWC), including the two US sires born in 2008 and 2010.

Discussion

Here, we report the clinical, histopathological, and genetic findings of the first *CACNA1S*-homozygous HO calf in Europe to be diagnosed with severe muscle weakness and recumbency. The calf's early inability to maintain a quadrupedal stance, marked muscle atrophy, and tremors, together with its pedigree, are consistent with the recently reported *CACNA1S*-related form of early-onset muscle weakness syndrome in the global HO cattle population.

In humans, multiple variants in the *CACNA1S* gene are reported to be associated with malignant hyperthermia susceptibility and hypokalemic periodic paralysis.[9, 16] Additionally, an association of *CACNA1S* variants with further human muscle disorders like thyrotoxic periodic paralysis, hypercreatinemia and statin-associated myopathy has been proposed (OMIM: 114208).[16] More recently, two new cases were reported showing a phenotype combining congenital myopathy with early-onset episodic weakness, closely resembling the homozygous Swiss HO calf case presented here.[1] Both human patients exhibited neonatal hypotonia, muscle weakness, and delayed walking, with episodic weakness emerging in infancy and persisting thereafter.[1] Genetic analysis revealed two novel pathogenic *CACNA1S* variants as cause in each case.[1]

The clinical progression observed in the present calf, including its initial ability to acquire a quadrupedal stance with assistance followed by rapid deterioration, mirrors the course reported in 21 of the 34 affected calves in the original study describing the MW in which 61 % of cases were euthanized.[6] These findings support our assessment of a poor to fatal prog-

nosis in the current case. Notably, 21 % of the reported cases were described as partially recovered; however, the study provides no definition of "recovery" and includes no follow-up on the subsequent development of these calves.[6]

Neurological assessment of the calf reported here revealed partially reduced reflexes and proprioception, suggesting that the primary deficit lies in muscle function rather than peripheral nerve integrity. This pattern supports the hypothesis that the observed weakness arises from an ion channel dysfunction causing a neuromuscular disorder.[4]

Histopathological examination of the affected calf revealed marked variability in fiber diameter, exceeding what would be expected for the young age of the patient,[14] as well as the presence of swollen, rounded fibers and fibers with centrally located nuclei.

Given the animal's young age, these fibers may also represent newly forming, immature myofibers, in addition to early regenerating fibers arising from prior degeneration.[2] However, in the context of the complex pathological phenotype and the pronounced heterogeneity in centrally nucleated fiber cross-sectional areas, this feature likely constitutes an intrinsic histopathological hallmark of the underlying congenital myopathy.

In skeletal muscle, action potential propagation initiates contraction through calcium-dependent excitation–contraction coupling.[7] This process requires voltage-gated calcium channels in the dihydropyridine receptor (DHPR) and the ryanodine receptor type 1 (RyR1), a ligand-gated calcium channel in the sarcoplasmatic reticulum.[7] The DHPR α1s subunit is enriched in junctional membrane fractions of the transverse (T-) tubules, where it colocalizes with the plasma-membrane Ca^{2+}-ATPase and the Na^{+}/Ca^{2+} exchanger, both responsible for calcium extrusion.[15] T-tubules align with the terminal cisternae of the sarcoplasmic reticulum to form triads.[15] Depolarization of the sarcolemma promotes DHPR–RyR1 coupling at the triad, triggering RyR1 opening, Ca^{2+} release into the sarcoplasm, and subsequent contraction.[7] Impairment of DHPR function could therefore disrupt this calcium influx sequence, leading to incomplete muscle contractions and compromised function[15] explaining the observed phenotype in the MW-affected calf. Additionally, the presence of inflammatory infiltrates likely represents secondary changes due to persistent recumbency and mechanical stress, potentially preceding fibrosis.

Future studies with larger cohorts and longitudinal follow-up are warranted to further elucidate the pathophysiology of this new disorder.

Based on the clinical presentation, several differential diagnoses were considered before confirming the calf's homozygosity for the *CACNA1S* variant. Based on the CBC, white muscle disease and anemia were considered unlikely (Supplementary Table S1). Additionally, spinal cord trauma was considered improbable, as there was no indication of injury. The diagnosis by exclusion supported *CACNA1S*-related MW as the most likely diagnosis, which was subsequently confirmed by genetic testing of the calf and its parents.

To date, knowledge of the spread of the MW causing allele remains limited. In the US HO population, the allele frequency was reported at 4,8 % [3], whereas in Poland, 19 % of 50 HO breeding sires, all related to a known MW carrier, were shown to be heterozygous carriers.[11] By comparison, the allele frequency observed in our study was relatively low. Furthermore, we identified carriers in the SF population for the first time. Nevertheless, the number of carriers should not be underestimated, as the continued, uncontrolled propagation of this harmful allele could result in more homozygous-affected calves unless appropriate breeding strategies are implemented.

Conclusion

This case report expands the phenotypic characterization of the recently reported *CACNA1S*-related MW disorder in cattle and provides a valuable reference for clinicians and breeders managing similar cases. The case underscores the importance of early genetic testing in suspicious calves with congenital disorders to guide both clinical care and breeding decisions. Confirmed homozygosity for the *CACNA1S* variant suggests a poor prognosis, however instances of recovery have been described.[5]

Although the allele frequencies of other MW variants in the Swiss HO and SF dairy cattle populations are relatively low, heterozygous carriers occasionally appear in the breeding population. If individual genotypes are not considered during mating, these genetic defects can be passed on, as mating between heterozygous parents can result in affected offspring. To safeguard animal welfare and prevent economic losses, it is essential to monitor carrier status in breeding programs and avoid risk matings. Comprehensive genotyping of the breeding population, combined with the careful selection of breeding animals and the use of digital mating planning tools (Erbfehlerampel), can help to limit the spread of known genetic defects and reduce the occurrence of affected animals.

Acknowledgements

This study was financially supported by the Arbeitsgemeinschaft Schweizerischer Rinderzüchter (ASR), Zollikofen, Switzerland, the Federal Office for Agriculture (FOAG), Bern, Switzerland. Joana Jacinto is supported in part by the Faculty Clinical Research Platform (FCRP) of the Vetsuisse Faculty of the University of Bern.

First European case of recessive *early-onset muscle weakness* syndrome in a Holstein calf

B. A. Weber et al.

Premier cas européen de syndrome de *faiblesse musculaire précoce* récessive chez un veau Holstein

Le syndrome de faiblesse musculaire précoce (MW) est une maladie génétique chez les bovins Holstein, décrite pour la première fois aux États-Unis en 2022 et causée par une variante du gène *CACNA1S* transmise selon un mode récessif. Ce rapport documente le premier cas confirmé de MW chez un bovin Holstein en Europe. Une génisse Holstein suisse âgée de 17 jours a été présentée pour une faiblesse progressive entraînant une incapacité à marcher et à se lever sans aide. L'examen clinique a révélé une atrophie musculaire généralisée, des tremblements, une base de sustentation élargie et une incapacité à se lever sans aide. Les analyses hématologiques et biochimiques étaient normales, à l'exception d'une légère monocytopénie et d'une créatinine plasmatique réduite. L'analyse histopathologique des muscles semi-tendineux et semi-membraneux a révélé une variabilité prononcée de la taille des fibres, des fibres hypertrophiques arrondies, de petites fibres à noyaux centraux, une légère infiltration mononucléaire et une augmentation du tissu conjonctif, résultats compatibles avec une altération myopathique chronique. L'analyse généalogique a révélé que la génisse atteinte était consanguine et pouvait être reliée à deux porteurs américains de la MW, ce qui suggère une transmission récessive. Le test génétique de ce cas a confirmé l'homozygotie pour le gène *CACNA1S*, alors que les deux parents étaient hétérozygotes. Une estimation de la fréquence de cet allèle défectueux dans la population Holstein suisse se monte à 0,56 % et à 1,07% chez Swiss Fleckvieh. La MW doit être envisagée comme diagnostic différentiel chez les jeunes veaux de ces deux races présentant des signes de décubitus et de faiblesse et doit faire l'objet d'un dépistage génétique en conséquence.

Mots clés: bovins, anomalie génétique, perte d'élevage, trouble récessif, décubitus, sélection

Primo caso europeo di sindrome *da early-onset muscle weakness (MW)* recessiva in un vitello Holstein

La sindrome da debolezza muscolare a esordio precoce (Muscle Weakness, MW) è una malattia genetica dei bovini Holstein, descritta per la prima volta negli Stati Uniti nel 2022, causata da una variante a trasmissione recessiva del gene *CACNA1S*. Questo lavoro documenta il primo caso confermato di MW in un bovino Holstein in Europa. Un vitello femmina Holstein svizzero di 17 giorni è stato presentato per debolezza progressiva e l'incapacità di alzarsi senza assistenza. L'esame clinico ha evidenziato atrofia muscolare generalizzata e tremori, una postura a base allargata e l'incapacità di assumere la stazione quadrupedale senza aiuto. Gli esami ematologici e biochimici non hanno mostrato anomalie significative, ad eccezione di una lieve monocitopenia e di una riduzione della concentrazione plasmatica di creatinina. L'esame istopatologico dei muscoli semitendinoso e semimembranoso ha evidenziato una marcata variabilità delle dimensioni delle fibre muscolari, fibre arrotondate e ipertrofiche, piccole fibre con nuclei centrali, una lieve infiltrazione mononucleare e un aumento del tessuto connettivo. Questi reperti sono compatibili con alterazioni miopatiche croniche. L'analisi genealogica ha mostrato che il vitello affetto era consanguineo e che la sua ascendenza poteva essere ricondotta a due portatori statunitensi della variante MW, suggerendo una modalità di trasmissione recessiva. L'analisi genetica ha confermato l'omozigosi per la variante del gene *CACNA1S* nel vitello affetto e l'eterozigosi in entrambi i genitori. La frequenza di questo allele deleterio nella popolazione Holstein svizzera è pari allo 0,56 % e all'1,07% nella razza Swiss Fleckvieh. La MW dovrebbe essere considerata una diagnosi differenziale nei vitelli che presentano decubito persistente e segni di debolezza muscolare e dovrebbe essere confermata mediante appropriati test genetici.

Parole chiave: sindrome da debolezza muscolare a esordio precoce, difetto ereditario, decubito persistente, bovini, difetto genetico recessivo, selezione genetica

Literaturnachweis

[1] Aburahma, S. K., Rousan, L. A., Shboul, M., Biella, F., Lucchiari, S., Comi, G. P., Meola, G., & Pagliarani, S. (2024). Case report: Dihydropyridine receptor (CACNA1S) congenital myopathy, a novel phenotype with early onset periodic paralysis. Frontiers in Neurology, 15, 1359479. doi: 10.3389/fneur.2024.1359479

[2] Aiello, D., Patel, K., & Lasagna, E. (2018). The myostatin gene: an overview of mechanisms of action and its relevance to livestock animals. Animal Genetics, 49, 505–519. doi: 10.1111/age.12696

[3] Al-Khudhair, A., VanRaden, P. M., Null, D. J., Neupane, M., McClure, M. C., & Dechow, C. D. (2024). New mutation within a common haplotype is associated with calf muscle weakness in Holsteins. Journal of Dairy Science, 107, 3768–3779. doi: 10.3168/jds.2023-24121

[4] Benarroch, L., Bonne, G., Rivier, F., & Hamroun, D. (2024). The 2024 version of the gene table of neuromuscular disorders (nuclear genome). Neuromuscular Disorders, 34, 126–170. doi: 10.1016/j.nmd.2023.12.007

[5] Ciacia, M. G., & Phipps, A. J. (2025). Early-onset muscle weakness syndrome (MW) in an Australian Holstein calf. Australian Veterinary Journal, 103, 298-303. doi: 10.1111/avj.13431

[6] Dechow, C. D., Frye, E., & Maunsell, F. P. (2022). Identification of a putative haplotype associated with recumbency in Holstein calves. Journal of Dairy Sciences Communications, 3, 412-415. doi: 10.3168/jdsc.2022-0224

[7] Dulhunty, A. F., Haarmann, C. S., Green, D., Laver, D. R., Board, P. G., & Casarotto, M. G. (2002). Interactions between dihydropyridine receptors and ryanodine receptors in striated muscle. Progress in Biophysics and Molecular Biology, 79, 45–75. doi: 10.1016/S0079-6107(02)00013-5

[8] Genossenschaft swissherdbook Zollikofen. (2025). Genetische Marker und Erbfehler – das Wichtigste in Kürze ! Retrieved May 11, 2026, from https://www.swissherdbook.ch/de/dienstleistungen/genetik/genomische-selektion/genetische-marker

[9] Hopkins, P. M., Rüffert, H., Snoeck, M. M., Girard, T., Glahn, K. P. E., Ellis, F. R., Müller, C.R., Urwyler, A., & European Malignant Hyperthermia Group (2015). European Malignant Hyperthermia Group guidelines for investigation of malignant hyperthermia susceptibility. British Journal of Anaesthesia, 115, 531–539. doi: 10.1093/bja/aev225

[10] Inokuma, H., Maezawa, M., Miyazaki, Y., Ogino, A., Watanabe, K. I., & Kobayashi, Y. (2025). A clinical case of CACNA1S-related muscle weakness in a Holstein calf with congenital astasia diagnosed by a genotyping test of stored blood. The Journal of Veterinary Medical Science, 87, 28–31. doi: 10.1292/jvms.24-0308

[11] Kamiński, S. (2024). Muscle Weakness – new genetic defect transmitted to Polish Holstein-Friesian cattle. Polish Journal of Veterinary Sciences, 27, 651–653. doi: 10.24425/pjvs.2024.152956

[12] Leuenberger, T., Jacinto, J. P. G., Seefried, F. R., & Drögemüller, C. (2024). BLIRD – eine neue genetische Erkrankung beim Holsteinrind in der Schweiz. Schweizer Archiv für Tierheilkunde, 166, 511–518. doi: 10.17236/sat00433

[13] Nicholas, F. W., Tammen, I., & Sydney Informatics Hub. (2025). Online Mendelian Inheritance in Animals (OMIA) [dataset]. doi: https://doi.org/10.25910/2AMR-PV70

[14] Rehfeldt, C., Te Pas, M. F. W., Wimmers, K., Brameld, J. M., Nissen, P. M., Berri, C., Valente, L.M.P., Power, D.M, Picard, B., Stickland, N.C. & Oksbjerg, N. (2011). Advances in research on the prenatal development of skeletal muscle in animals in relation to the quality of muscle-based food. I. Regulation of myogenesis and environmental impact. Animal, 5, 703–717. doi: 10.1017/S1751731110002089

[15] Sacchetto, R., Margreth, A., Pelosi, M., & Carafoli, E. (1996). Colocalization of the dihydropyridine receptor, the plasma-membrane calcium ATPase isoform 1 and the sodium/calcium exchanger to the junctional-membrane domain of transverse tubules of rabbit skeletal muscle. European Journal of Biochemistry, 237, 483–488. doi: 10.1111/j.1432-1033.1996.0483k.x

[16] Sangkuhl, K., Dirksen, R. T., Alvarellos, M. L., Altman, R. B., & Klein, T. E. (2020). PharmGKB summary: very important pharmacogene information for CACNA1S. Pharmacogenetics and Genomics, 30, 34–44. doi: 10.1097/FPC.0000000000000393

[17] Weber, B. A., Leuenberger, T., Hauser, M., Bousmar, J. C. F., Gurtner, C., Seefried, F. R., Drögemüller, C. & Jacinto, J. G. P. (2025). Übersicht über bekannte und neue Erbfehler sowie deren Verbreitung bei Swiss Fleckvieh Rindern. Schweizer Archiv für Tierheilkunde, 167, 280–291. doi: 10.17236/sat00452

Korrespondenzadresse

Cord Drögemüller
Institute of Genetics, Vetsuisse Faculty, University of Bern, Switzerland
Bremgartenstrasse 109a
CH-3012 Bern
Email: cord.droegemueller@unibe.ch