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Clinical genetics of selected neuromuscular disorders in Swiss dairy cattle

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04.12.2025, Bern

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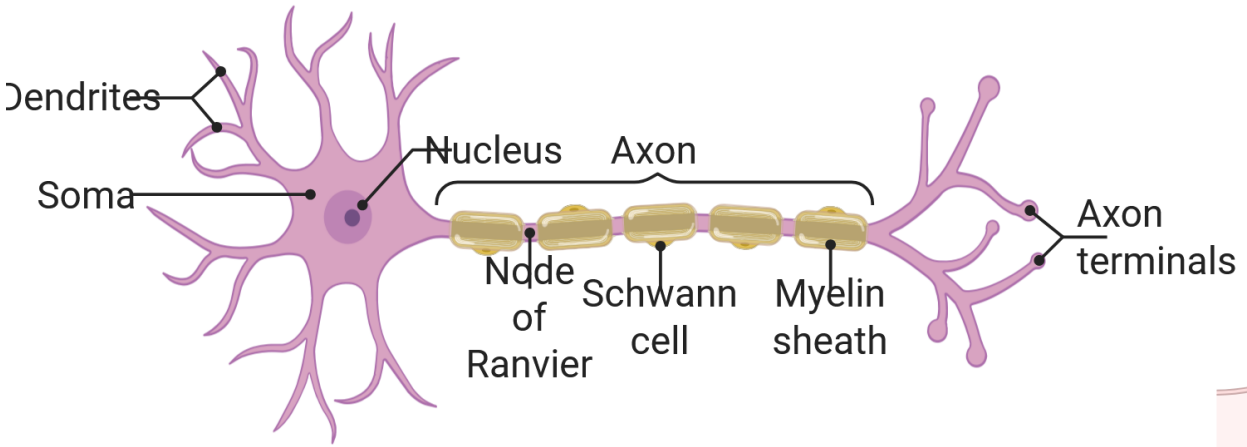
The motor unit

Motor neuron

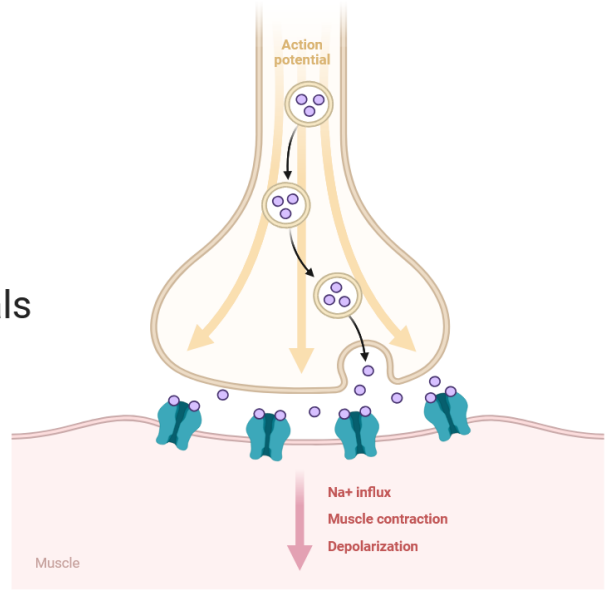


Spinal muscular atrophy (SM) in BS

Myelinated axon

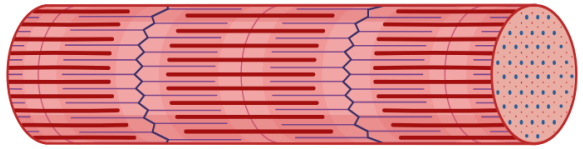
Charcot–Marie–Tooth (CMT) in HO & JE

Neuromuscular junction



Congenital myasthenic syndrome in Braham

Muscle fiber

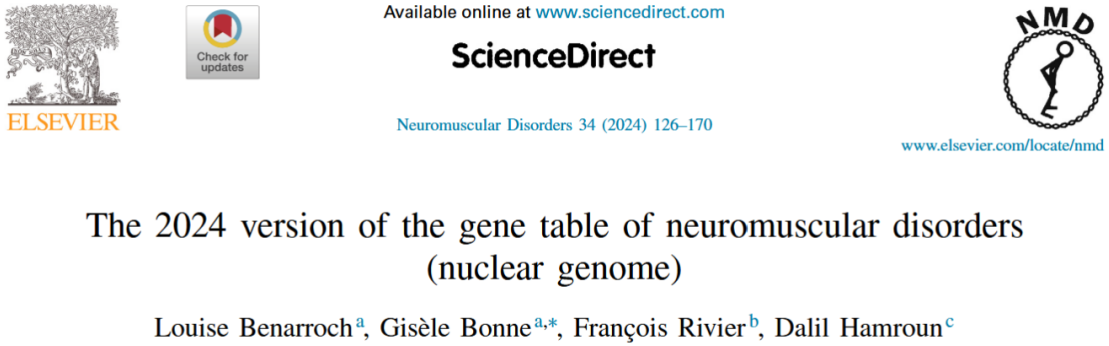


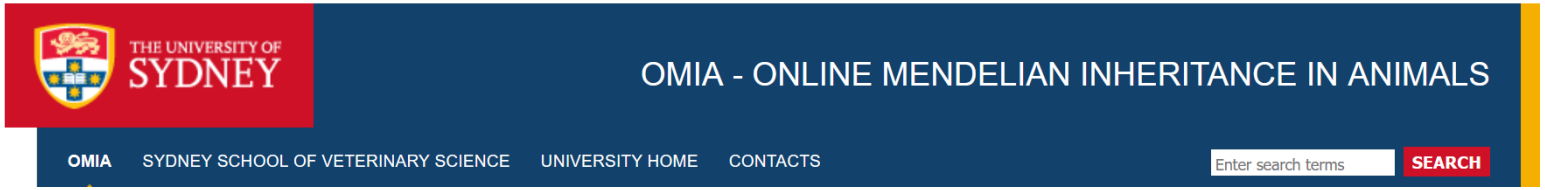
Muscle weakness (MW) in HO

What are neuromuscular disorders (NMDs)?

Heterogeneous group of disorders

- Reduction or loss of the ability to perform voluntary motor movement
- Human medicine → 16 groups; >1200 disorders
  - Congenital myopathies
  - Channelopathies
  - Hereditary ataxias
- Veterinary medicine → ?
  - **Cattle: >25 different NMDs with known causal variant**





NMDs that are no longer of importance for Swiss dairy cattle

Sidonia Glatthard
Master thesis

Erbfehler beim Schweizer Braunvieh – eine Übersicht

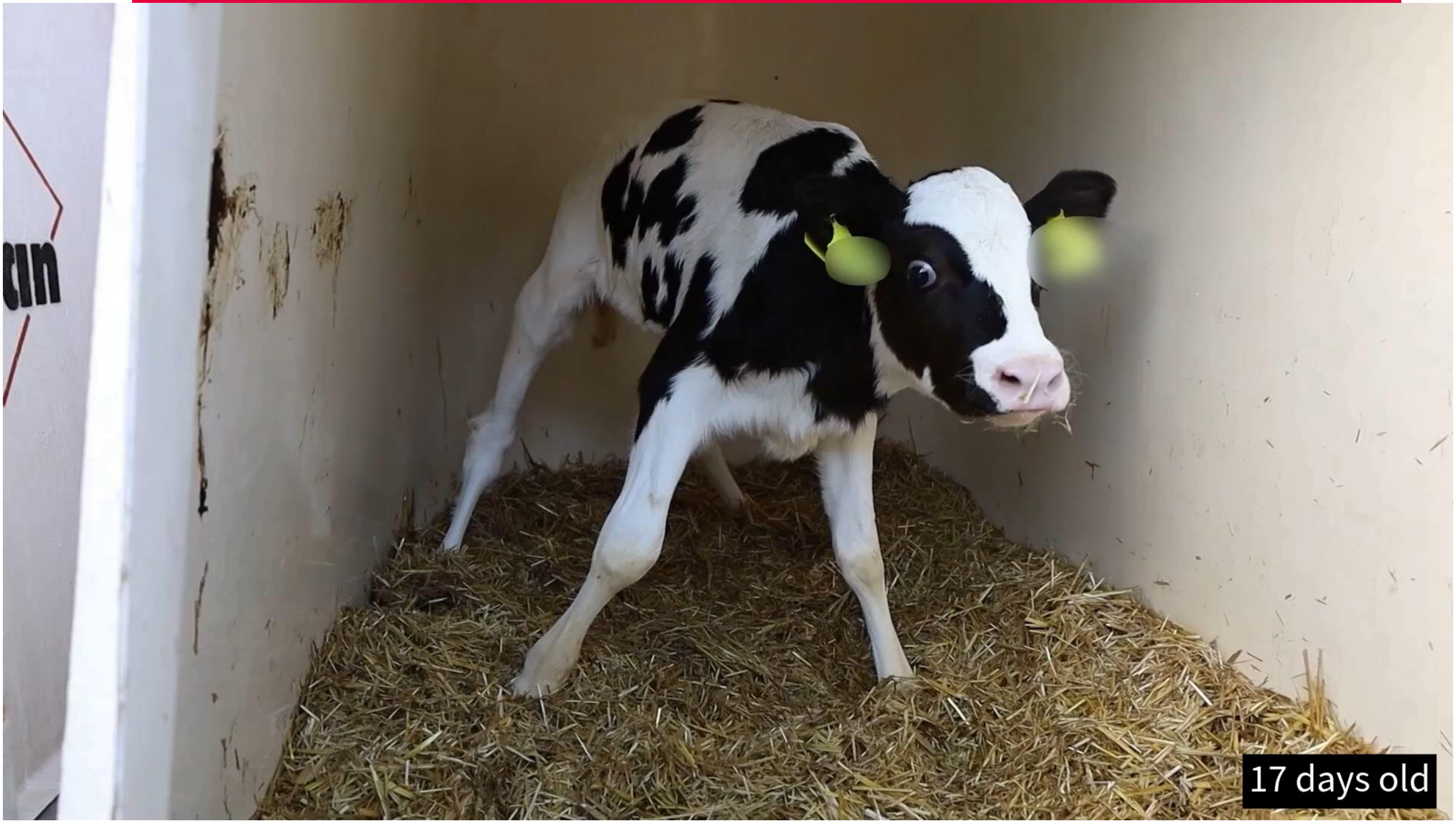
S. Glatthard[1], F. R. Seefried[2], A. Gentile[3], J. G. P. Jacinto[1,4], C. Drögemüller[1]

	Arachnomelie (AR)		Spinale Muskelatrophie (SM)		Spinale Dysmyelinisierung (SD)		Weaver-Syndrom (WE)	
	BS	OB	BS	OB	BS	OB	BS	OB
Frei (F)	47964	7968	42893	8303	43143	8304	43224	8305
Heterozygot (C)	10	0	379	3	137	1	57	0
Homozygot (S)	0	0	0	0	0	0	0	0
Defektallel-frequenz (%)	<0,01 %	0,00 %	0,44 %	0,02 %	0,16 %	0,01 %	0,07 %	0,00 %

Recent Holstein congenital NMD: muscle weakness (MW)

- ***CACNA1S***
  - Missense variant
  - α1S subunit of the L-type voltage-dependent calcium channel in skeletal muscle
- **Congenital myopathy/Channelopathy**
- **Clinical signs**
  - muscle weakness & atrophy
  - inability to quadrupedal stance without assistance
- **Poor prognosis**
  - Mortality rate > 50% before six weeks of age

Cohort	MWF	MWC	MWS	AF (%)	HWE p-value
HO	17'921	213	1	0.59	0.47
SF	2'689	85	0	1.53	1


17 days old

Novel juvenile-onset NMD in Brown Swiss: hereditary ataxia

- ***LIPC***
  - Missense variant
  - hepatic lipase
- **Hereditary ataxias**
- **Onset ± 2.5 years**
- **Clinical signs**
  - subconscious proprioceptive ataxia
  - postural & gait abnormalities
  - dyslipidemia

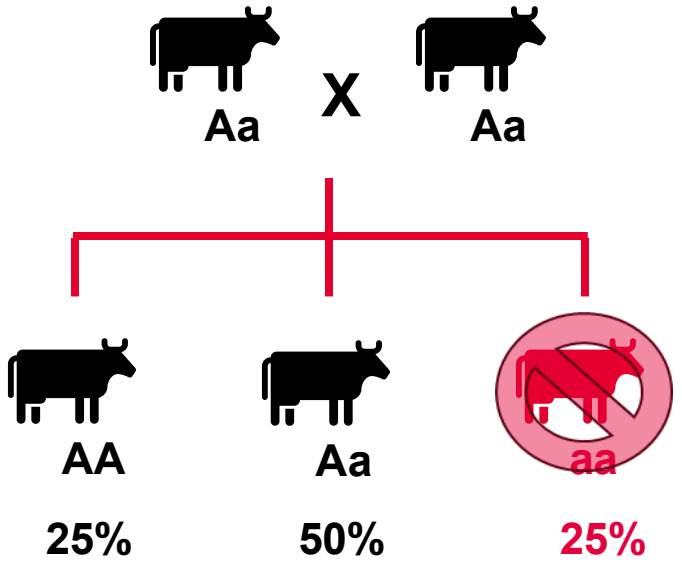
Bettina Weber
Doctoral thesis


Case 1
Age: 2.5 years

Novel juvenile-onset NMD in Brown Swiss: hereditary ataxia

Wildtype (AA)	heterozygous (Aa)	homozygous – expected (aa)	homozygous – real (aa)	Minor allele frequency (%)	Hardy-Weinberg Equilibrium p-value
4407	2280	199	16	17	3.98×10^{-24}

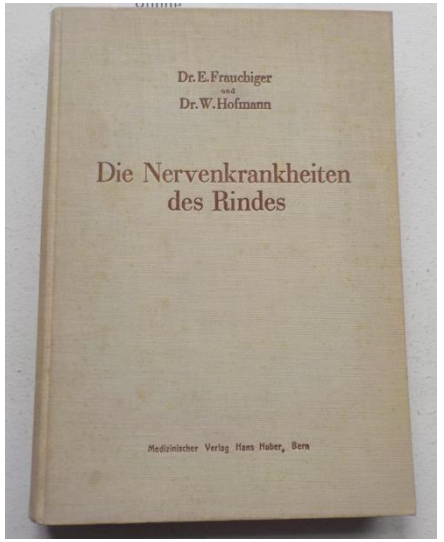
Significant **Hardy-Weinberg disequilibrium**



First take-home message

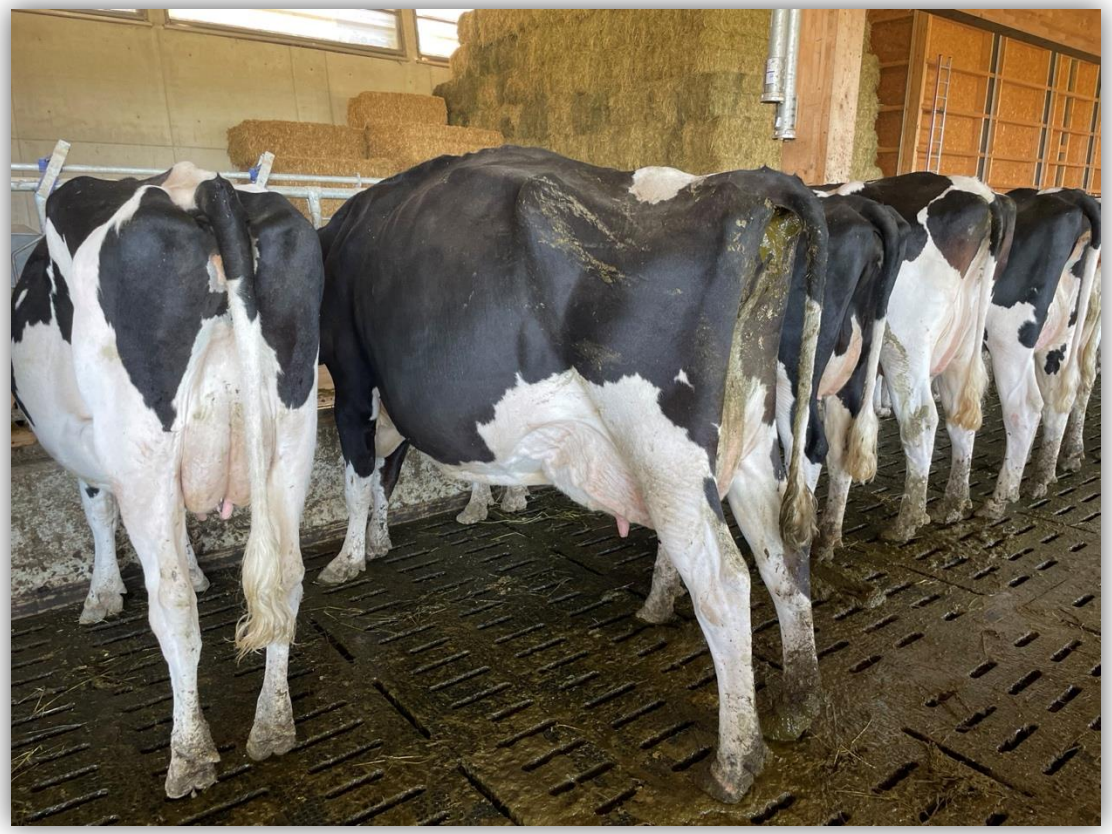
- Genetic NMDs are a **heterogenous group of disorders**
- Can be **congenital** or **occur later in life**
- Some NMDs are **simple** → one disease, one causal variant
  - Muscle weakness in Holstein
  - Hereditary ataxia in Brown Swiss

Bovine spastic syndrome (BSS): an NMD first reported in Bern 80 years ago, yet still unresolved



- **Progressive NMD**
- **Adult onset**
  - 3–7 years
- **Most striking clinical sign**
  - Recurrent reversible muscle spams of pelvic limbs
- **Various breeds affected**

  Holstein, Brown Swiss, Swiss Fleckvieh, Simmental, etc



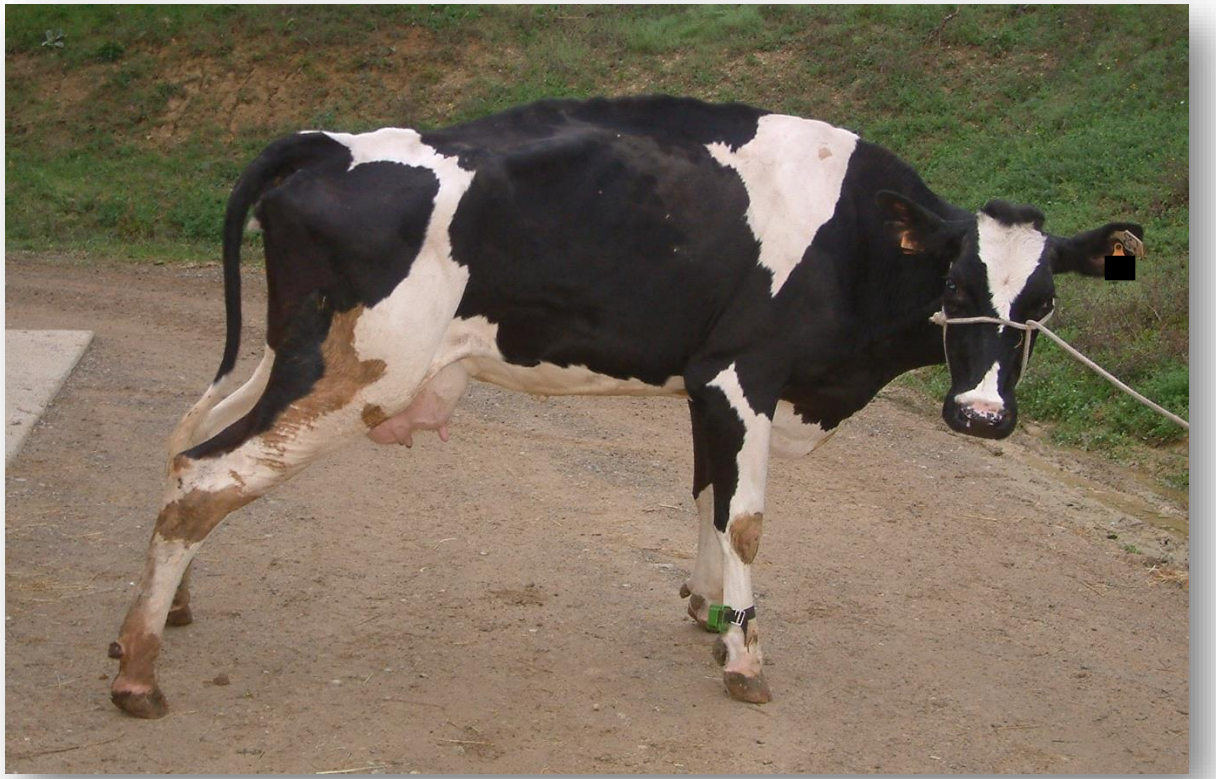
Brown Swiss
Male
5.5 years-old

Bovine spastic syndrome (BSS): clinically heterogenous

Clinical presentation

- Variable duration and number of episodes
- Variable severity
- Unilateral vs bilateral form
- Clinical signs are not the same in affected animals

Heterogeneous




What is the cause of BSS?
Not clear…
Monogenic?
Polygenic?
Epigenetics?
Recessive mode of inheritance?
Dominant mode of inheritance?

Bovine spastic syndrome (BSS): where are we now?

- **Etiology in Holstein**
  - Monogenic
    - 6 autosomal dominant variants in *MPEG1*, *LHX8*, *WHAMM*, *NGRN*, *ATP1A1*, *PCDH1*
    - 1 autosomal recessive in ***TOR3A***
  - Polygenic
    - Several significant QTLs but not clear
    - h^2 based on liability scale ~ 0.47
- **Prevalence**
  - Canada: ~ 4% in Holstein
- **BSS: a hidden threat to Swiss dairy cattle?**

nature › scientific reports › articles › article

Article | Open access | Published: 28 December 2024

Whole genome sequencing reveals candidate causal genetic variants for spastic syndrome in Holstein cattle

Joana G.P. Jacinto, Anna Letko, Irene M. Häfliger, Eylem Emek Akyürek, Roberta Sacchetto, Arcangelo Gentile & Cord Drögemüller

J. Dairy Sci. TBC
https://doi.org/10.3168/jds.2025-27026

Genetic insights into bovine spastic syndrome (Crampy) in Holstein dairy cattle

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Lactanet CANADIAN NETWORK FOR DAIRY EXCELLENCE — Milk Recording — Genetics

Crampy Project Update

August 14, 2024

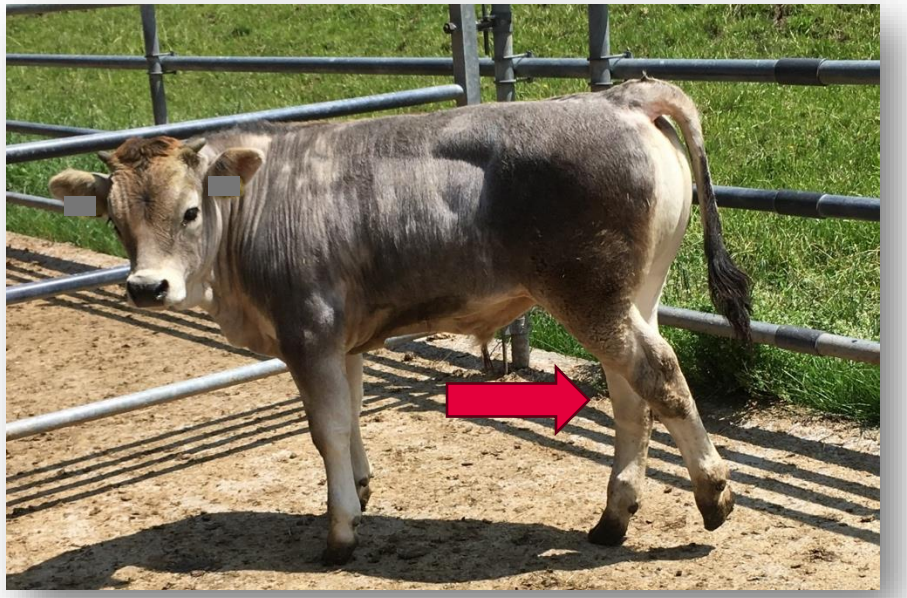
SWISS-BSS

Bovine spastic paresis (BSP): a century-old NMD also still unsolved

- **Progressive NMD**
- **Juvenile onset**
  - Early form: calves <6 months (more frequent)
  - Late form: manifests at 24–30 months of age
- **Most striking clinical sign**
  - Persistent hyperextension of the pelvic limb
  - 4 different severity grade
- **Various breeds affected**

  Brown Swiss, Grauvieh, Holstein, Swiss Fleckvieh, Simmental, etc
- **Etiology** → not clear!

Brown Swiss, female, 6 months-old, BSP grade 1



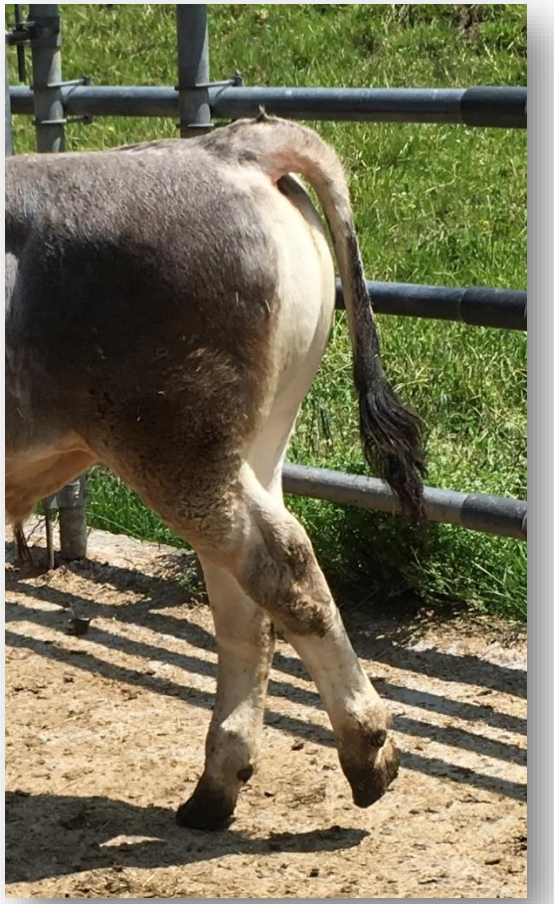
Grauvieh, male, 6 months-old, BSP grade 4

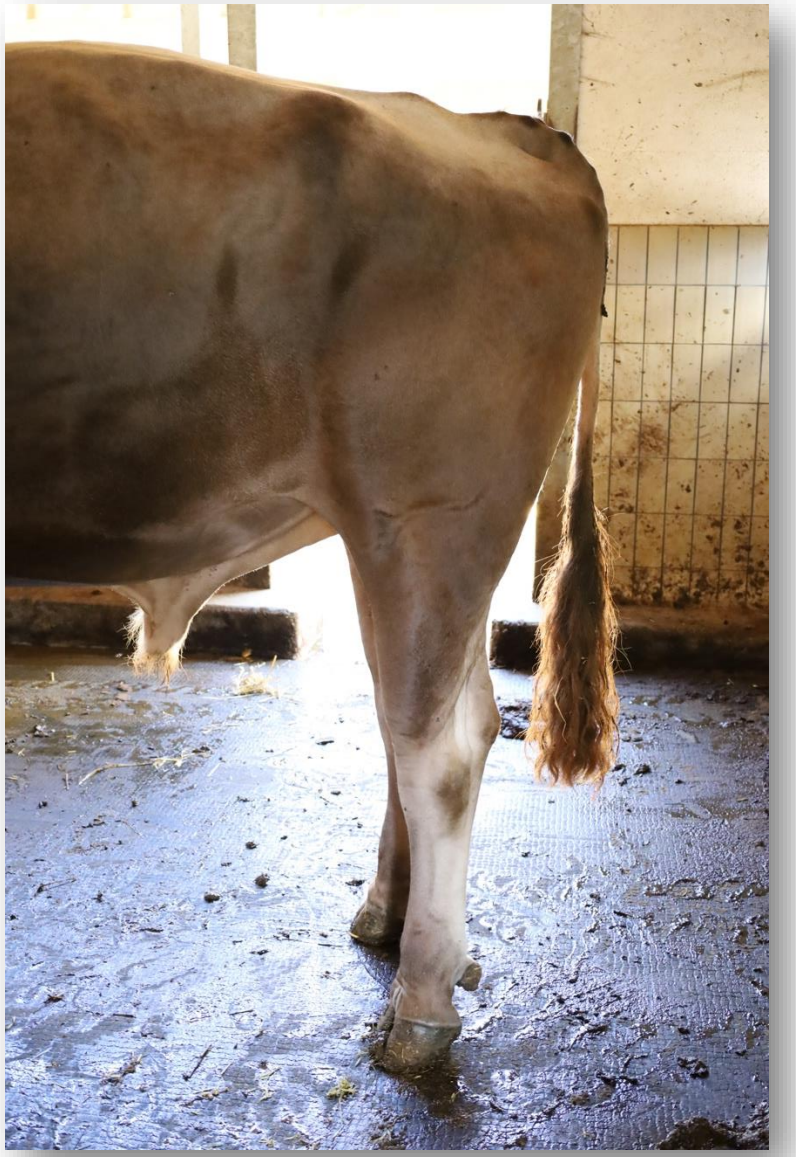
Bovine spastic paresis (BSP): clinically heterogenous

Clinical presentation

- Variable severity
- Unilateral vs bilateral form
- Clinical signs are not the same in affected animals

Heterogeneous





Bovine spastic syndrome (BSS) vs Bovine spastic paresis (BSP): distinct NMDs

BSS

vs

BSP

Second take-home message

- Some NMDs are **complex**
  - Different forms of one disorder → within and between breeds
  - Different MOI
  - Different affected genes and causal variants
  - Examples: **BSS** and **BSP**

- BSS and BSP are frequently misdiagnosed
  - **two different disorders**
  - both with **heterogenous presentation**

- NMDs negatively affect **welfare**, **productivity**, and **breeding potential**

Owners/breeders,

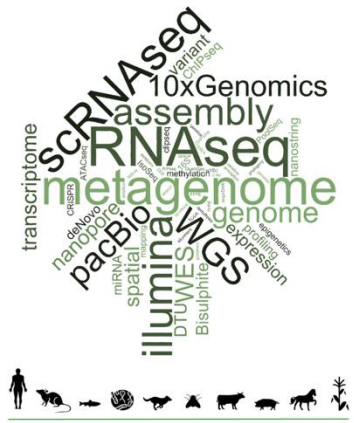
veterinarians, clinicians, pathologists,

bioinformaticians, laboratory technicians,

international collaborators,

local colleagues…

Interfaculty Bioinformatics Unit



Faculty Clinical Research Platform (FCRP)

ASR

Qualitas

swiss herdbook

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Thank you for your attention!

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Questions?

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Scan me!

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Bovine spastic syndrome (BSS) vs Bovine spastic paresis (BSP): distinct NMDs

Feature	Bovine Spastic Paresis (BSP)	Bovine Spastic Syndrome (BSS)
Age of onset	Juvenile	Adult
Clinical signs	Progressive hyperextension of the pelvic limb(s) and contraction of the Achilles tendon caused by persistent muscle spasms	Hyperextension of the pelvic limb(s) caused by recurrent, reversible clonic and tonic muscle cramps
Similarities	- Unilateral or bilateral pelvic limb affection - Often increased ankle joint angle - No recovery of clinical signs	