UNIVERSITÄT BERN

Numerous monogenic recessive disorders segregate in Swiss dairy populations

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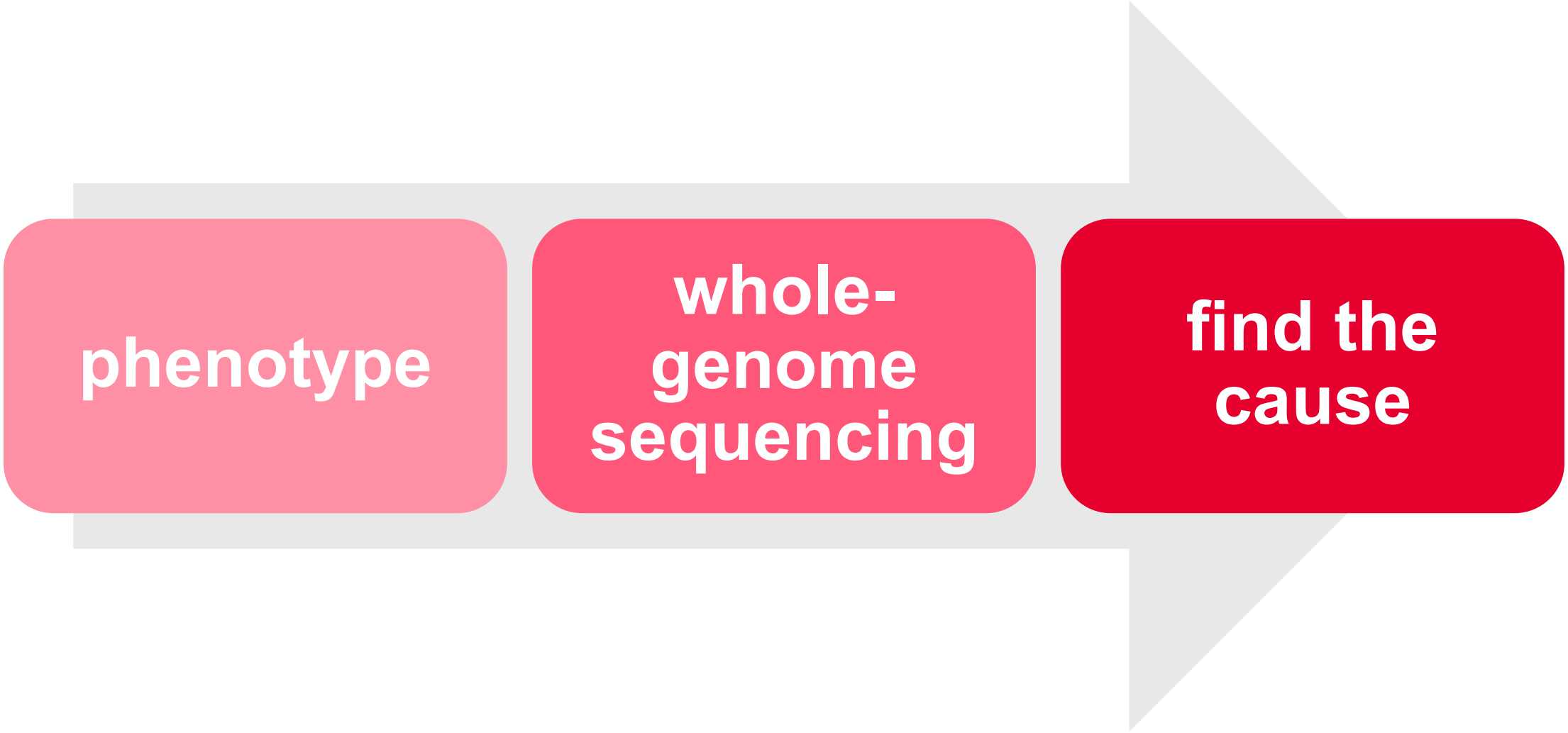
SABRE-TP

10. November 2021, Zürich

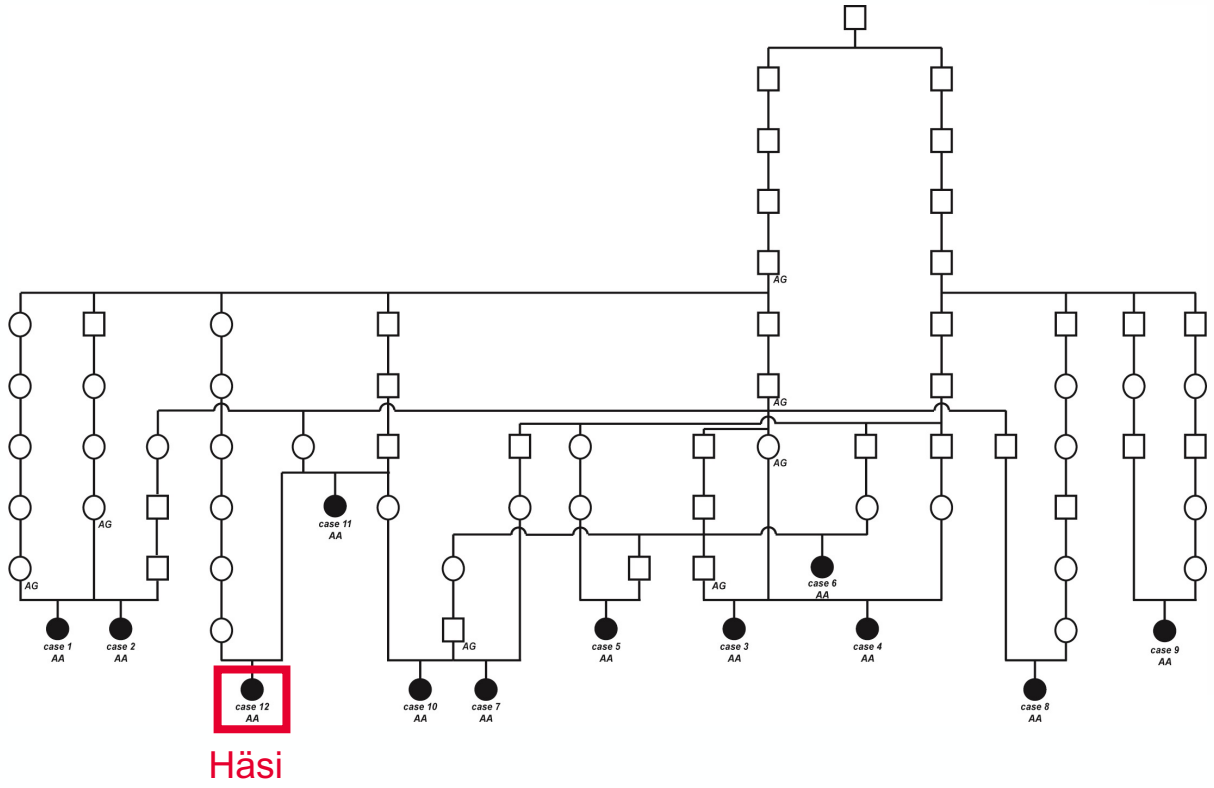
Forward genetics approach



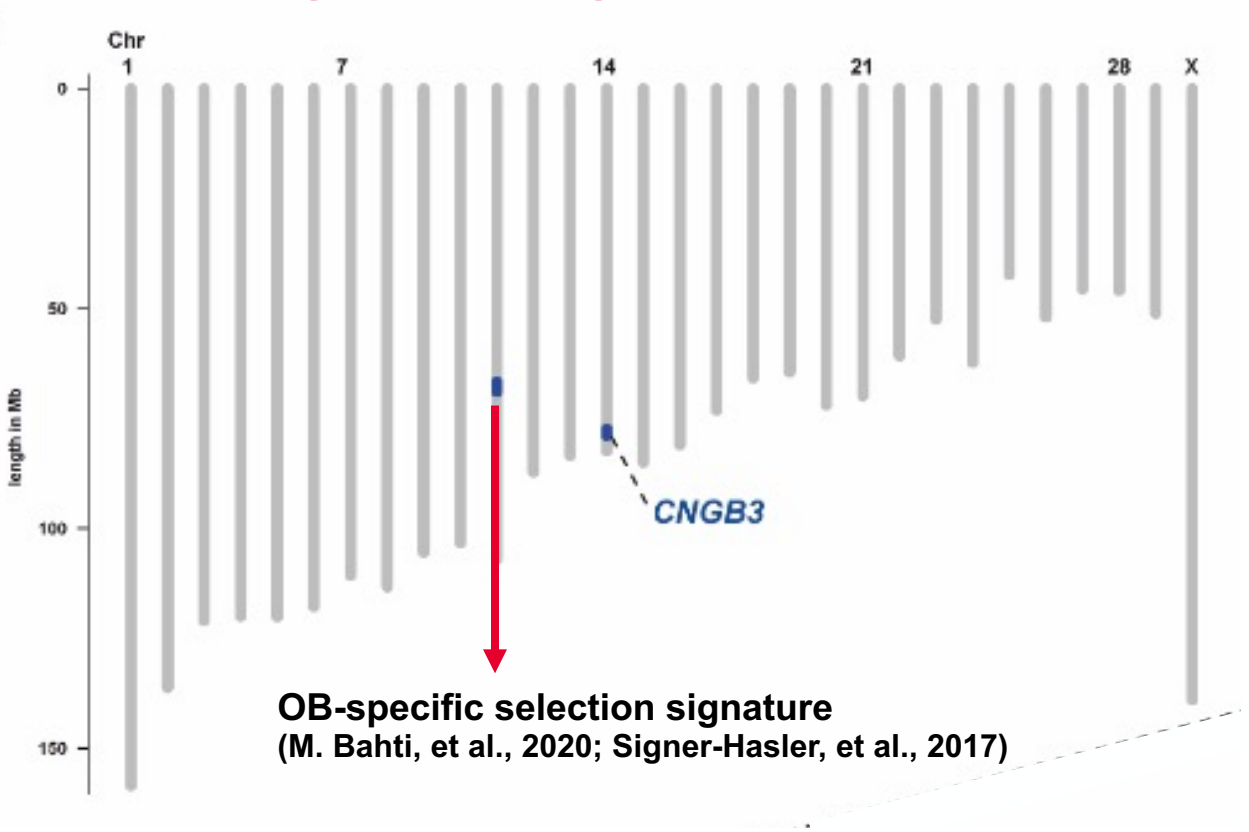
CNGB3-associated achromatopsia in Original Braunvieh

impaired vision similar to day-blindness in human (and dogs)

Genetic analysis: IBD mapping using 12 cases



Häsi

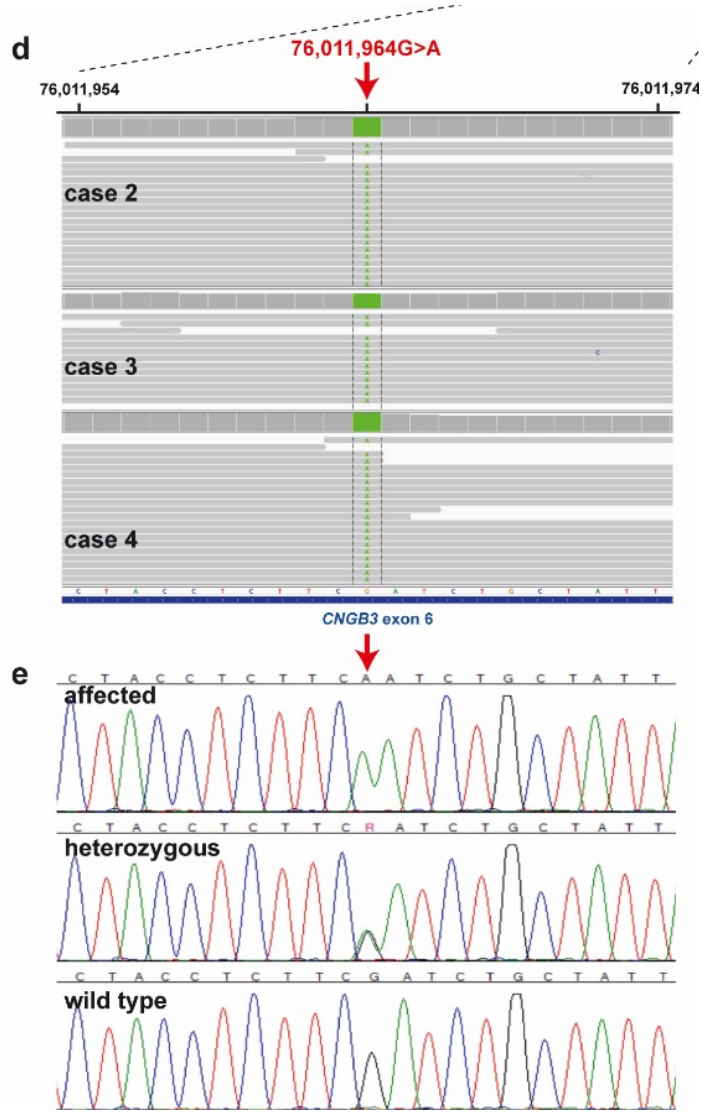


~2.5 Mb run of homozygosity on chromosome 14

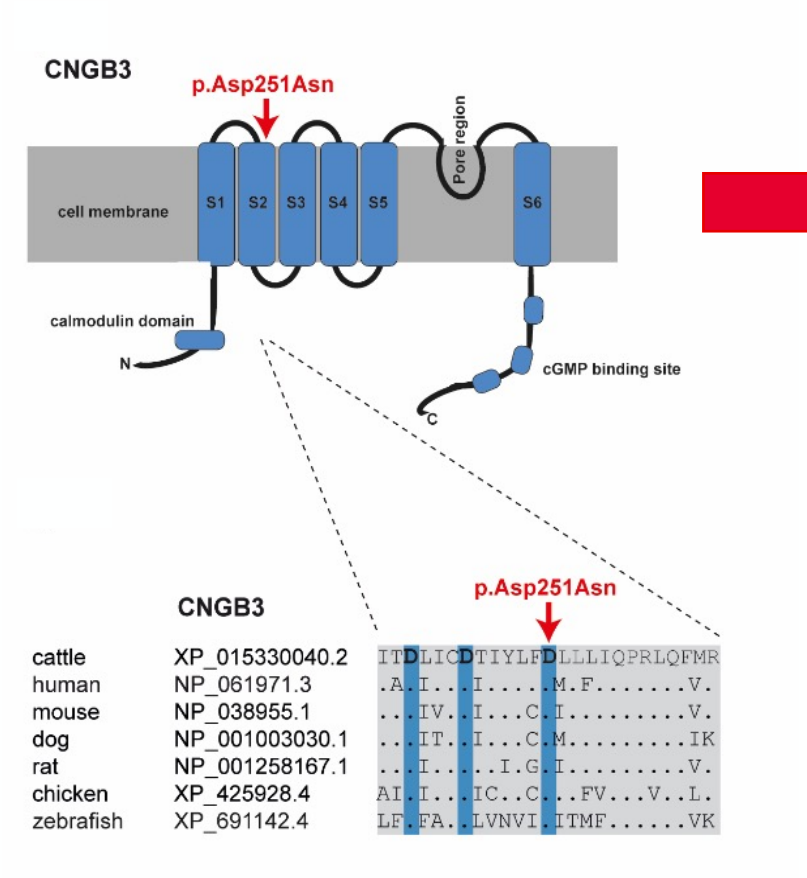
Candidate variant identification

- WGS data
  - 3 cases, their 3 dams and 2 sires
  - 567 control genomes
- Variant filtering:
  - 1/1 in the cases
  - 0/1 in all parents
  - 0/1 or 0/0 in all other animals

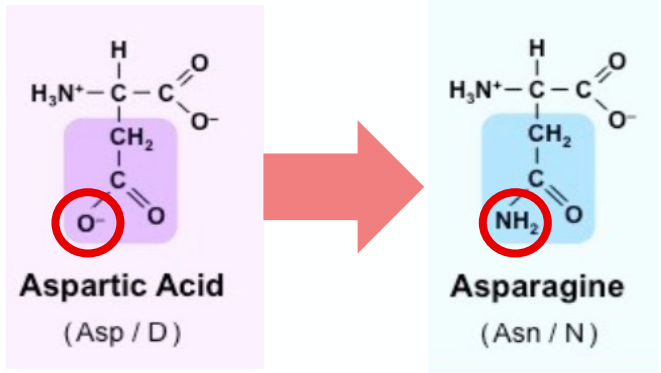
Chr 14:76011964 G>A
CNGB3:p.Asp262Asn



Validity of the *CNGB3* variant



impairing channel bio-genesis Asp/Asn mutations affect the electrostaticity within the S1-S4
(N. Tanaka, et al., 2014)



- **Allele frequency**
  - **0.099 in >2'950 Original Braunvieh**
  - **0.0015 in >15'000 Brown Swiss**

submitted

Article

***CNGB3* missense variant causes recessive achromatopsia in Original Braunvieh cattle**

Irene M. Häfliger[1*], Emma Marchionatti[2*], Michele Stengård[3*], Sonja Wolf-Hofstetter[1], Julia M. Paris[1], Joana G. P. Jacinto[4], Christine Watté[3], Katrin Voelter[5], Laurence M. Occelli[6], András M Komáromy[6], Anna Oevermann[7], Christine Goepfert[8], Angelica Borgo[9], Raphaël Roduit[9], Mirjam Spengeler[10], Franz R. Seefried[10] and Cord Drögemüller[1*]

APOB-associated cholesterol deficiency (CD) in Holstein

- 1.3kb ERV insertion in *APOB* linked to CDH
- Biologically incapable of digesting cholesterol in the intestine
- Clinical signs: asymptomatic diarrhea
- Calves mostly “starve” to death
- Allele frequency in Swiss Holstein population (2021) at **0.0612**

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics

SHORT COMMUNICATION

doi: 10.1111/age.12801

APOB-associated cholesterol deficiency in Holstein cattle is not a simple recessive disease

Irene Monika Häfliger*, Sonja Hofstetter*, Thomas Mock†, Manuela Hanna Stettler†, Mireille Meylan†, Kemal Mehinagic‡, Nadine Stokar-Regenscheit‡ and Cord Drögemüller*

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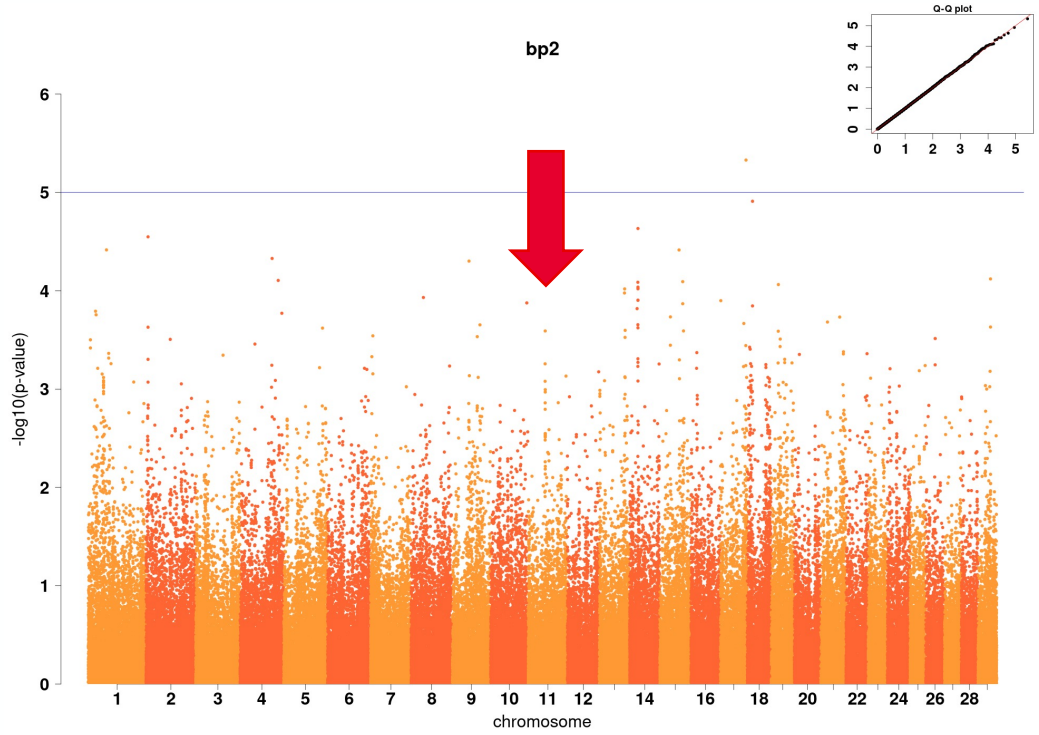
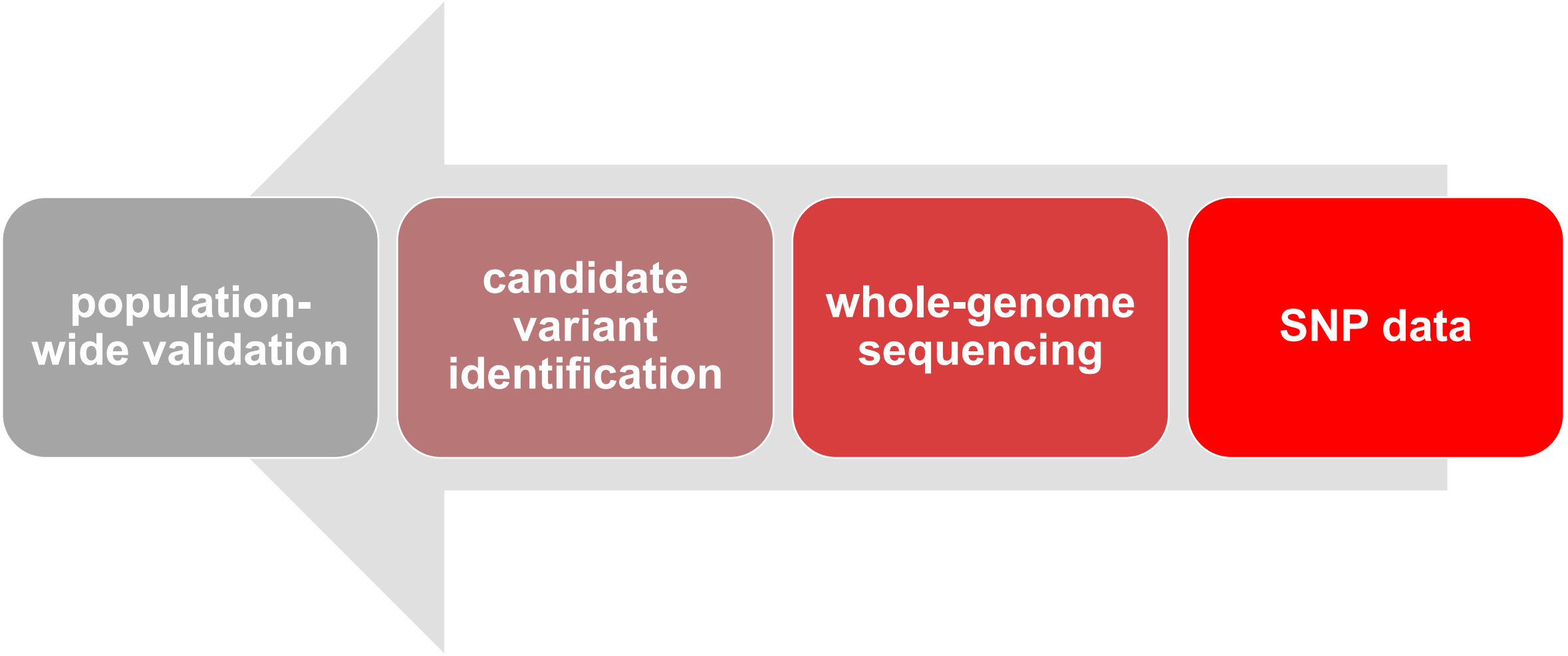
APOB-associated cholesterol deficiency (CD) in Holstein

- **Problem:** Co-dominant effect
- Sample calculation

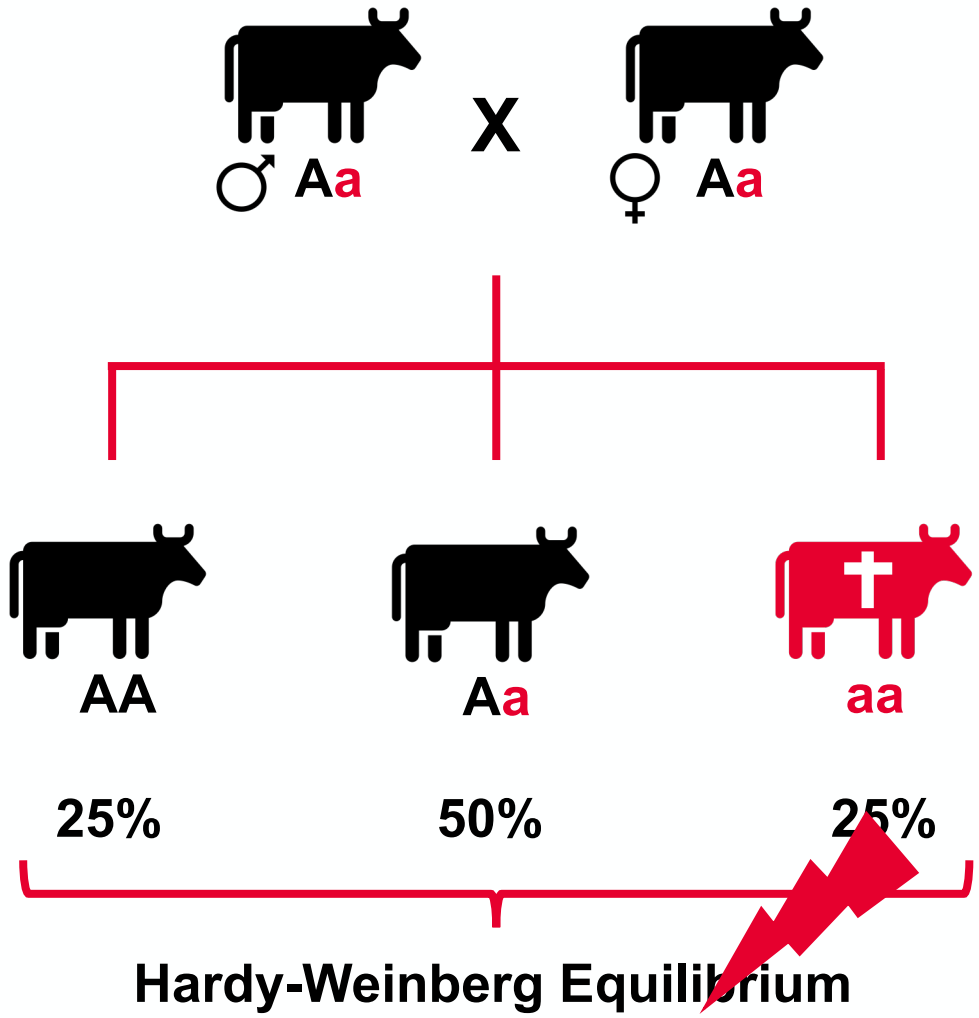
Assumption	# animals
Herdebooks (Population size)	250’000 healthy cows
Homozgous wt HWE	220’360
Homozgous carrier HWE	**935**
Heterozygous carrier HWE	28’705
Every 3rd heterozygous carrier shows symptoms	9’568
Every 10th heterozygous carrier dies due to the symptoms	**2’871**
sum	**3’806**



Reverse genetics approach

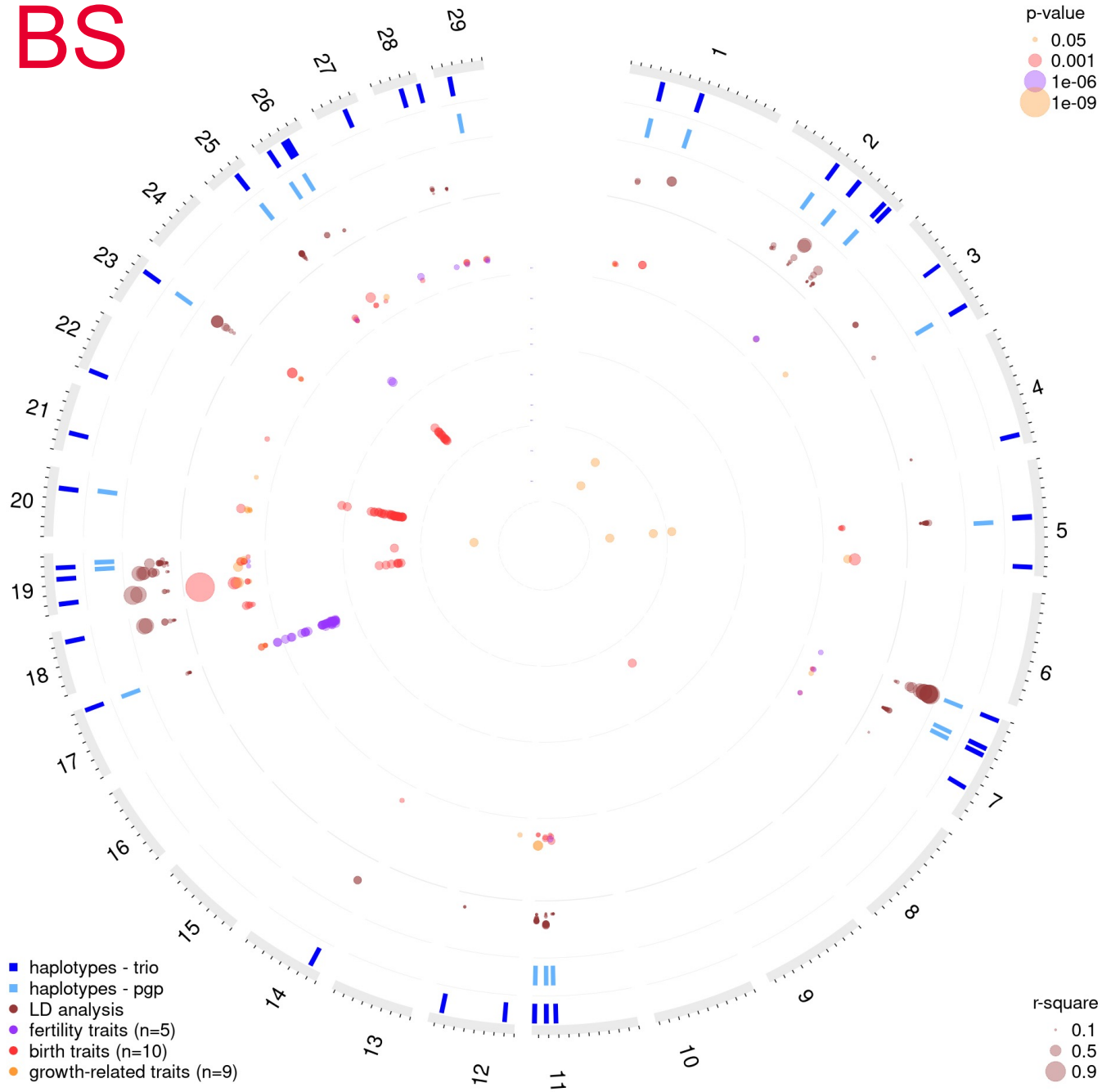


Mendelian Inheritance Theory of Recessive Variants



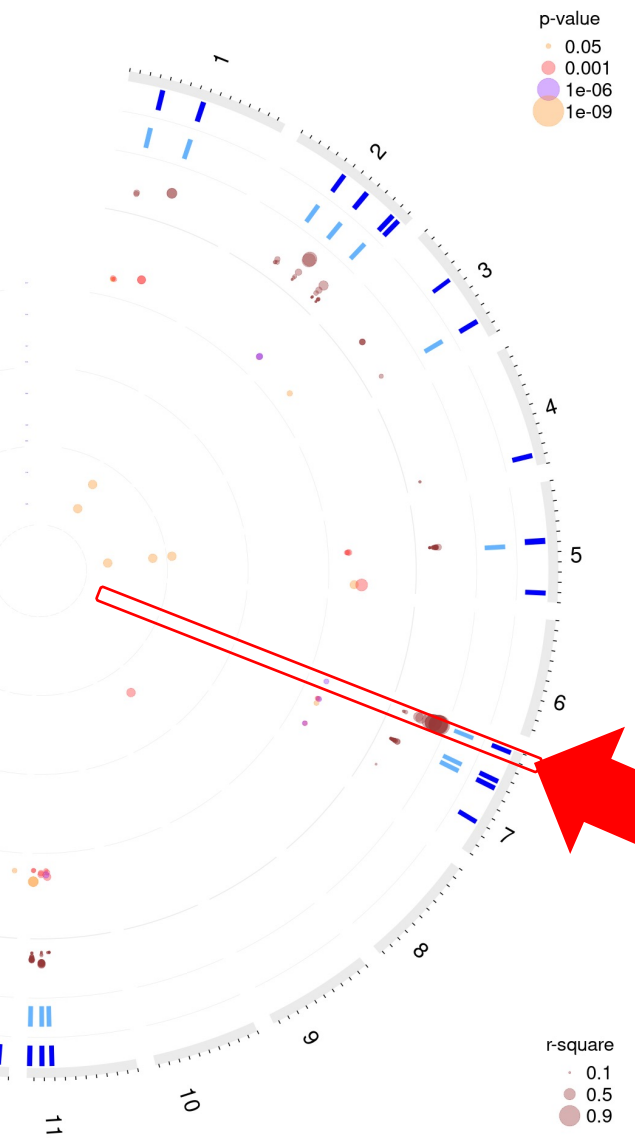
Missing of homozygous animals

Results – Overview BS



Häfliger I.M., Seefried F.R., Spengeler M. & Drögemüller C. **2021**. **Mining massive genomic data of two Swiss Braunvieh cattle populations reveals six novel candidate variants impairing reproductive success.** *Genetics Selection Evolution,* submitted.

BH14 in the spotlight



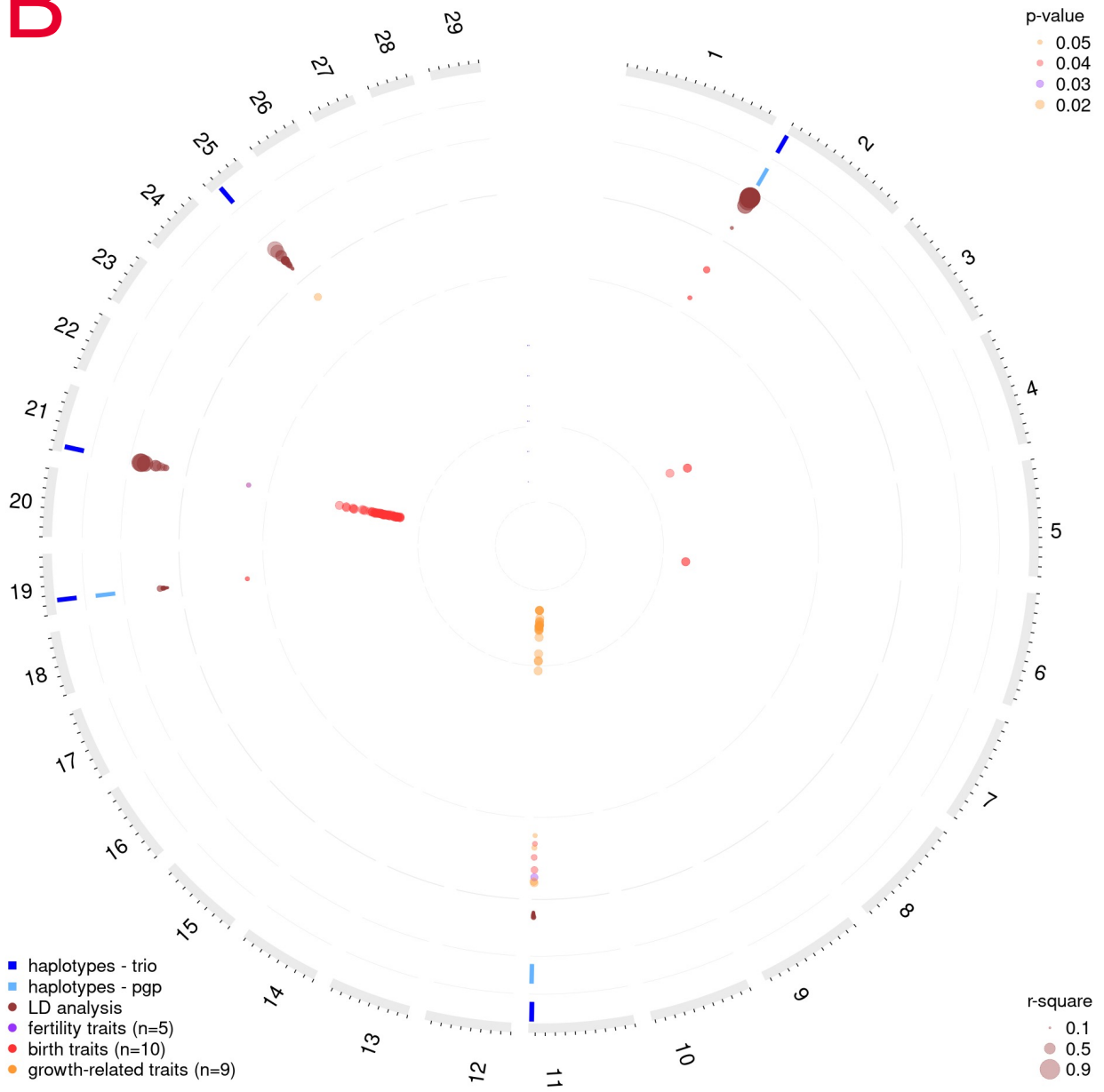
- **Haplotype:**
  - 0 of 45 expected homozygous animals
  - Allele frequency: 0.03
  - Associations:
    - interval first to last insemination, cows
    - interval calving to first service
    - fat cover
    - **heifer survival rate up to 458d**
- **Candidate causal variant:** Chr7 2996436 C>T ***MRPL55***: p.Arg57* (nonsense variant)
  - High LD with haplotype
  - NO homozygous animal in > 4’500 WGS
  - NO homozygous animal in > 13’000 custom array

BH14-associated *MRPL55* variant

- **Gene:** *MRPL55*
  - mitochondrial ribosomal protein L55
  - Gen function:
    - Essential role in the mitochondrial ribosomal complex
    - Protein binding enzyme
  - Associated disorder:
    - **Early embryonic death in homozygous knock-out mice** (Cheong et al. 2021)

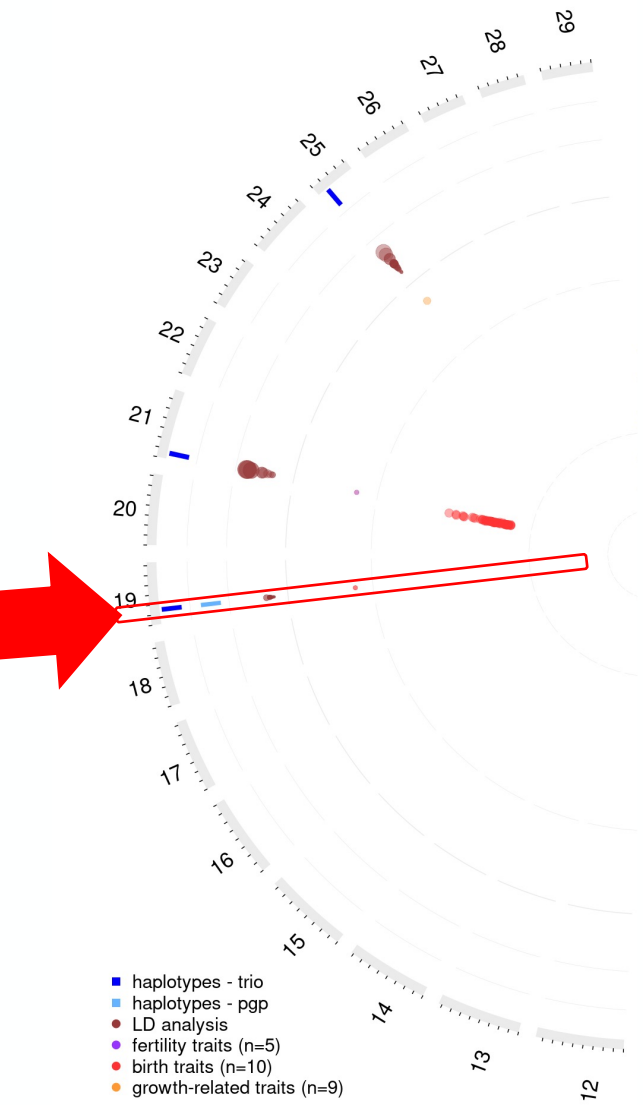
Hypothesis: homozygous embryos are non-viable and are aborted during early embryogenesis

Results – Overview OB



Häfliger I.M., Seefried F.R., Spengeler M. & Drögemüller C. **2021**. **Mining massive genomic data of two Swiss Braunvieh cattle populations reveals six novel candidate variants impairing reproductive success.** *Genetics Selection Evolution,* submitted.

OH6 in the spotlight



- **Haplotype:**
  - 0 of 15 expected homozygous animals
  - Allele frequency: 0.039
  - Association:
    - ⛔ percentage live birth, maternal

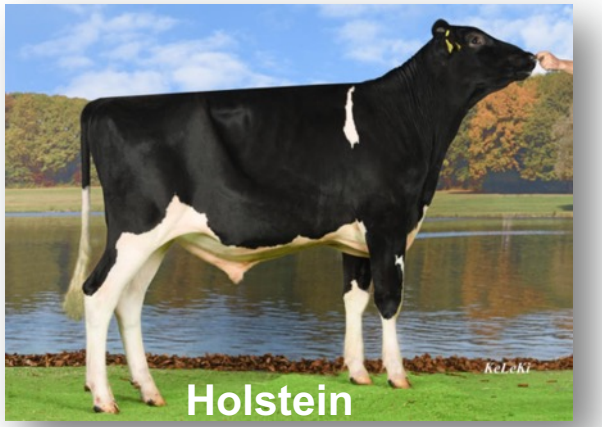
- **Candidate causal variant:**
  - Chr19:15080335 GGCACCT>G
    LIG3: p.Lys828fs (frame-shift variant; splice site)
  - perfect LD with haplotype
  - NO homozygous animal in > 4’500 WGS

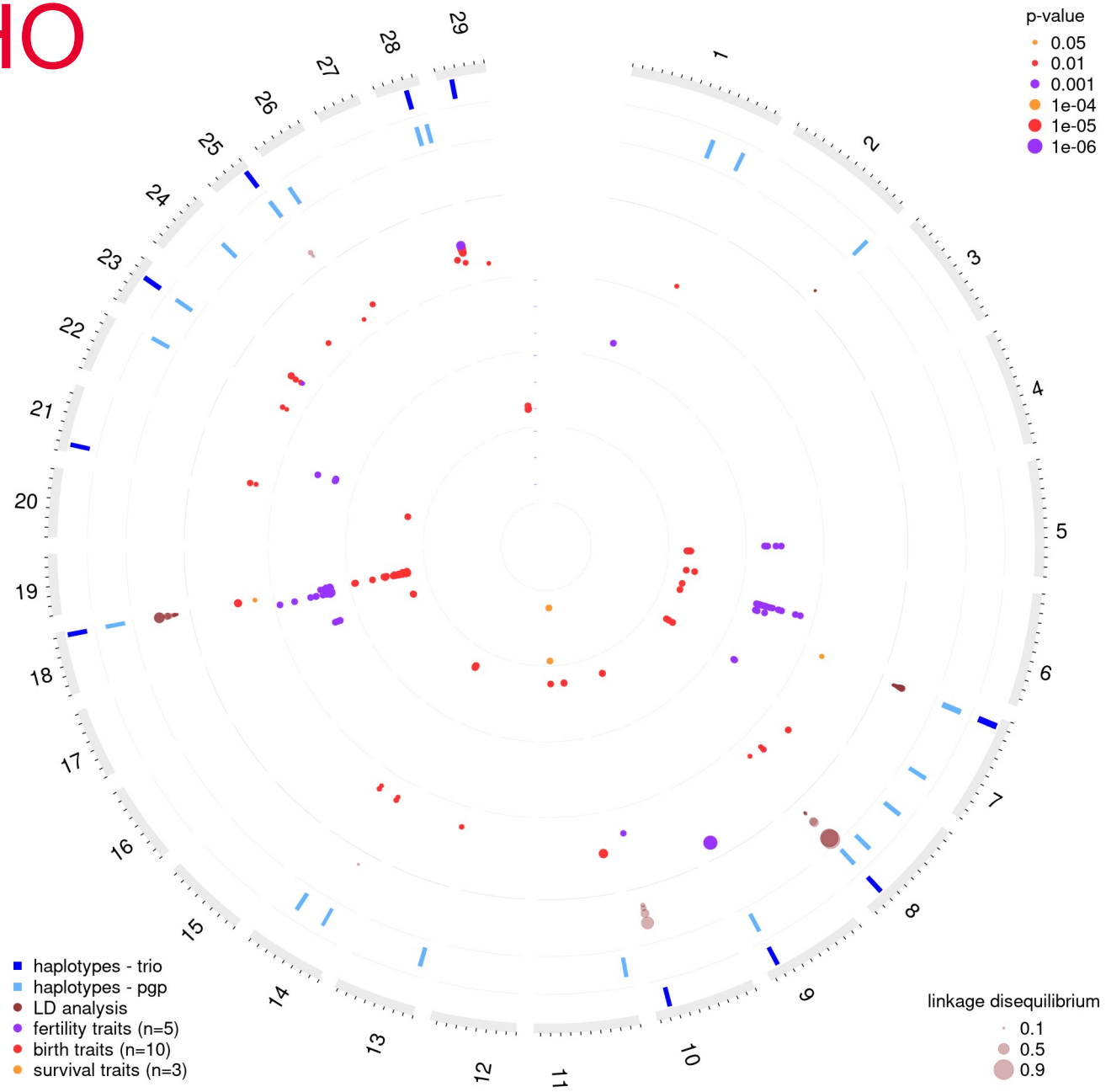
OH6-associated *LIG3* variant

- **Gene:** *LIG3*
  - DNA ligase 3
  - Gene function:
    - Repair of DNA strand breaks
    - Essential for repair of mitochondrial DNA
  - Associated disorders:
    - **Homozygous lethal in kock-out mice** (Shokolenko et al., 2013)

Hypothesis: homozygous embryos are non-viable and are aborted during early embryongenesis

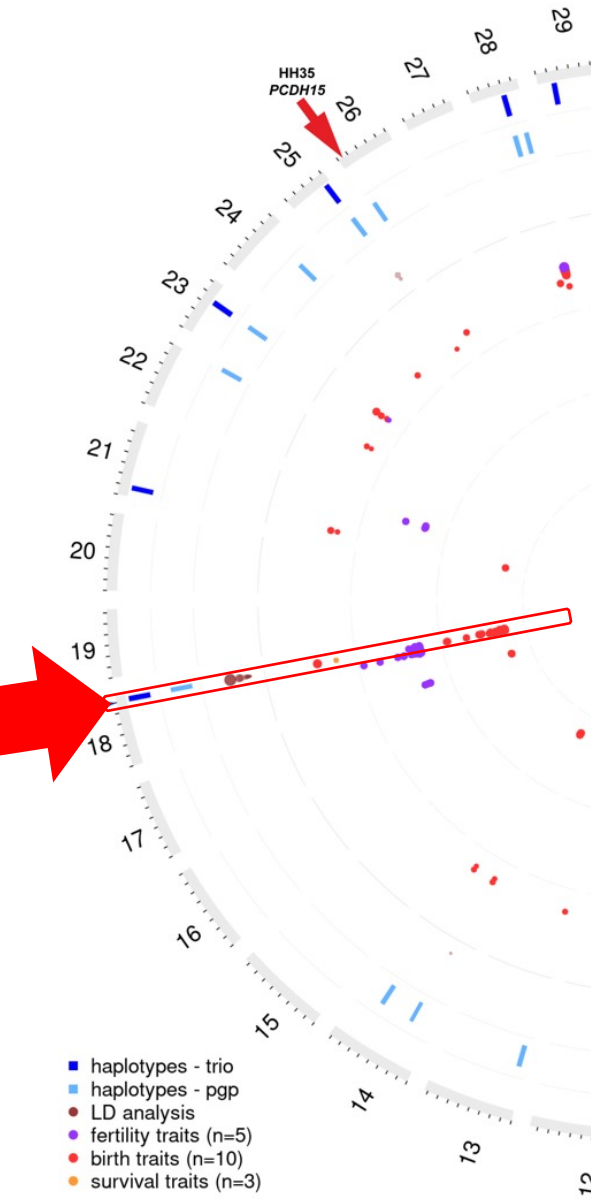
Results – Overview HO





Häfliger I.M., Spengeler M., Seefried F.R. & Drögemüller C. **2021**. **Four novel candidate causal variants for deficient homozygous haplotypes in Holstein cattle.** *Scientific Reports,* submitted.

HH13 in the spotlight



- **Haplotype:**
  - 1 of 17 expected homozygous animals
  - Allele frequency: 0.018
  - Associations: (including GWAS)
    - **Non-return rate**
    - **Interval first to last inseminaiton**
    - **Birth weight, direct**

2013

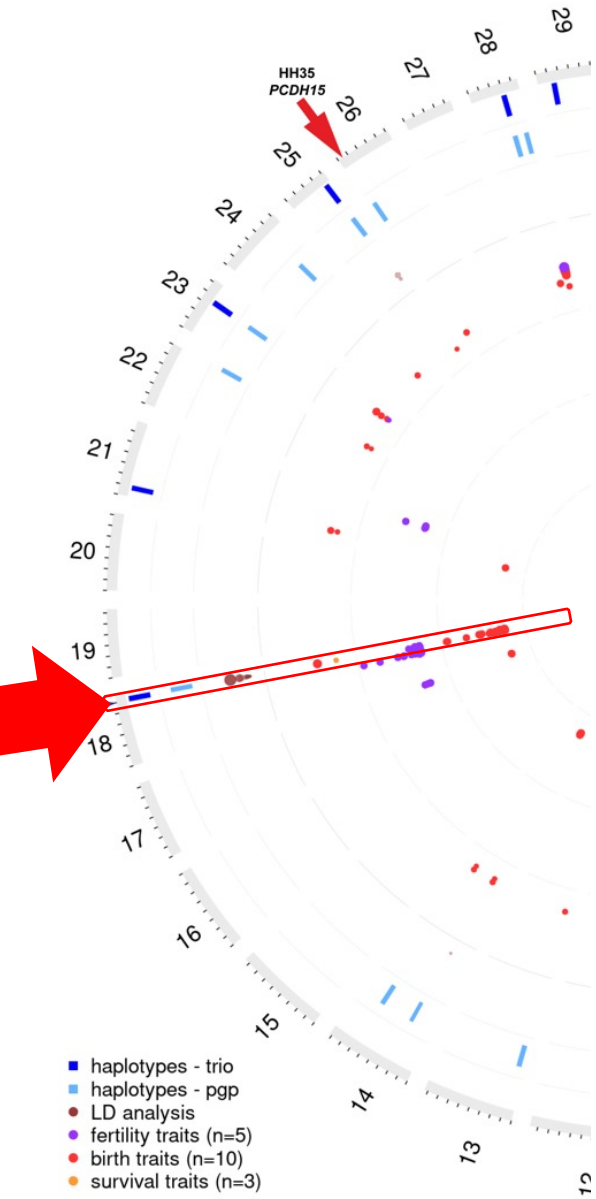
OPEN ACCESS Freely available online PLOS ONE

Detection of Haplotypes Associated with Prenatal Death in Dairy Cattle and Identification of Deleterious Mutations in GART, SHBG and SLC37A2

Sébastien Fritz[1,2], Aurelien Capitan[1,2], Anis Djari[3], Sabrina C. Rodriguez[2,3], Anne Barbat[2], Aurélia Baur[1,2], Cécile Grohs[2], Bernard Weiss[2], Mekki Boussaha[2], Diane Esquerré[4], Christophe Klopp[3], Dominique Rocha[2], Didier Boichard[2]*

1 UNCEIA, Genetics Team, Paris, France, **2** INRA, UMR1313 Animal Genetics and Integrative Biology, Jouy-en-Josas, France, **3** INRA, Sigenae, UR875 Biométrie et Intelligence Artificielle, Castanet-Tolosan, France, **4** INRA, GeT Genomics Facility, UMR444 Laboratoire de Génétique Cellulaire, Castanet-Tolosan, France

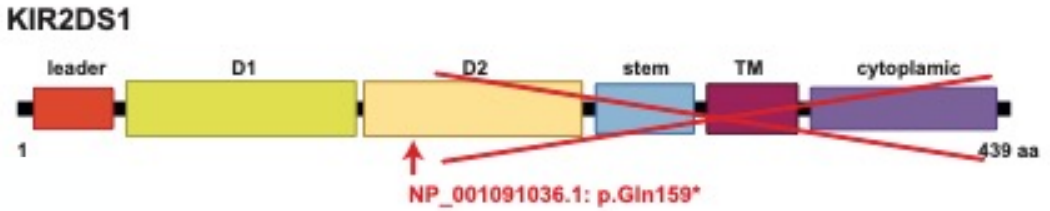
HH13 in the spotlight



- **Haplotype:**
  - 1 of 17 expected homozygous animals
  - Allele frequency: 0.018
  - Associations: (including GWAS)
    - **Non-return rate**
    - **Interval first to last inseminaiton**
    - **Birth weight, direct**

- **Candidate causal variant:** Chr18 62758881 G>A
- ***KIR2DS1****:* p.Gln159* (nonsense variant)
  - average LD with Haplotype
  - NO homozygous animals in > 4’200 WGS
  - NO homozygous animals in > 13’000 SWISScow

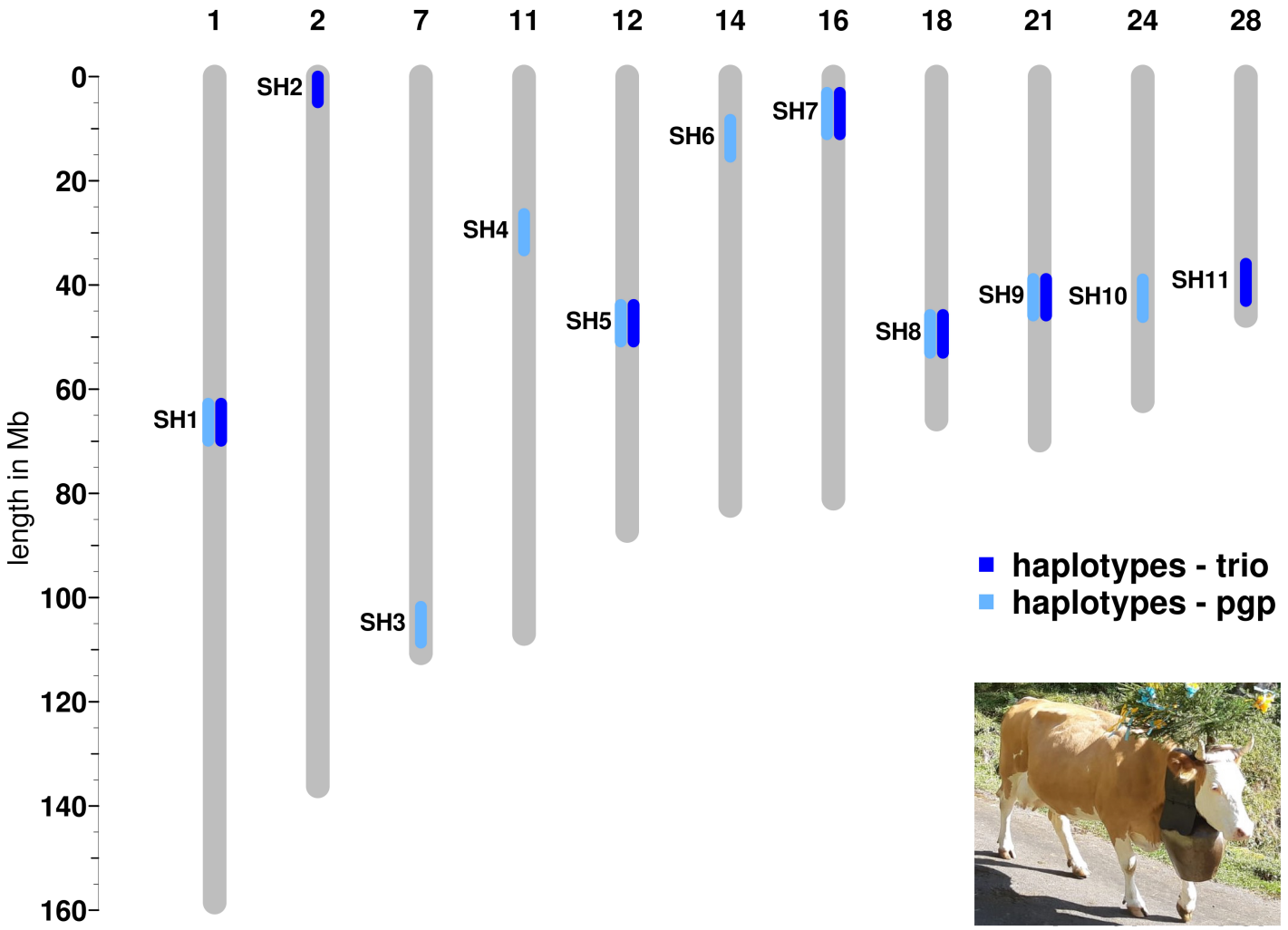
HH13-associated *KIR2DS1* variant



- **Gene:** *KIR2DS1*
  - killer cell immunoglobulin like receptor, two Ig domains and short cytoplasmic tail 1
  - Gene function:
    - Placentation success; embryonic growth
    - Immune system
  - Associated disorders:
    - **Pregnancy loss**
    - **Infections during pregnancy**

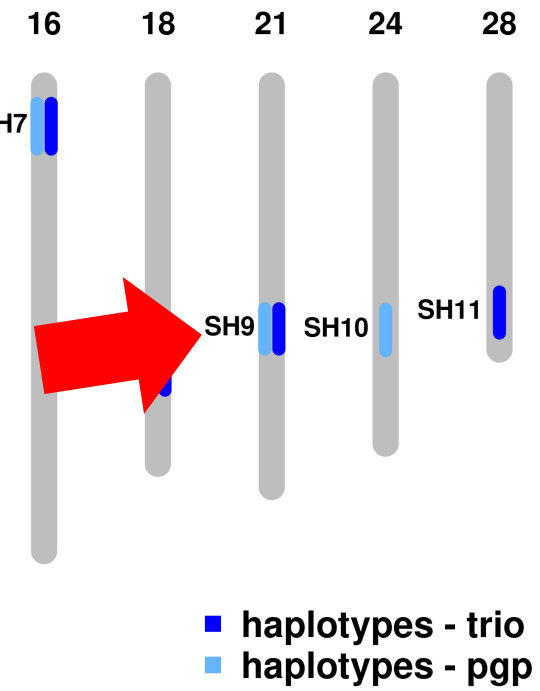
Hypothesis: homozygous embryos fuse not in the placenta and/or are aborted during early embryongenesis

Results – Overview SI



Häfliger I.M., Seefried F.R. & Drögemüller C. **2021**. **Reverse genetic screen for deleterious recessive variants in the local Simmental cattle population of Switzerland.** *Animals,* submitted.

SH9 in the spotlight

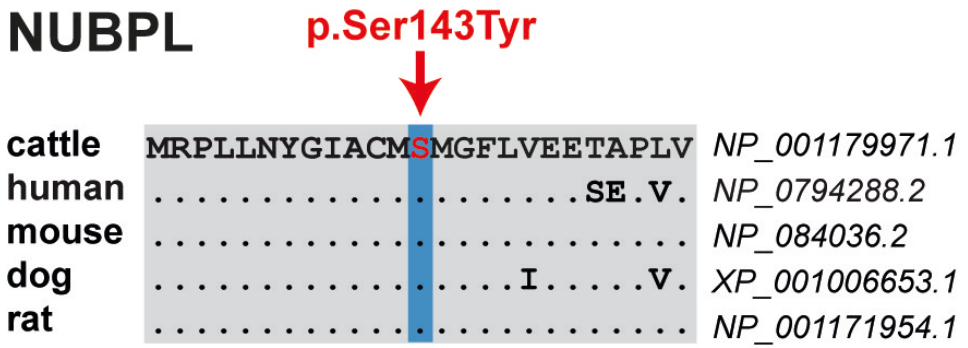


- **Haplotype:**
  - 2 of 19 expected homozygous animals
  - Allele frequency: 0.0433

- **Candidate causal variant:** Chr21 42154344 C>A
- ***NUBPL****:* p.Ser143Tyr (missense variant)
  - perfect LD with Haplotype
  - Highly conserved base and residue
  - NO homozygous animals in > 4’200 WGS

SH9-associated *NUBPL* variant

- **Gene:** *NUBPL*
  - nucleotide binding protein like
  - Gene function:
    - Assembly of the respiratory complex I
    - Immune system
  - Associated disorders:
    - **Mitochondrial complex I deficiency disorder (OMIM: 613621,618242)**
      - **Ataxia, spasticity, etc.**
    - **Homozygous lethal in kock-out mice (MGI:1924076)**



Hypothesis: homozygous embryos are non-viable and are aborted during early embryogenesis

Summary of selected causal variants

Phenotype / Haplotype	Breed	Associated gene	Allele / haplotype frequency
Cholesterol deficiency	Holstein	*APOB*	0.061
Ichthyosis	Scottish Highland	*DSP*	0.012
Achromatopsia (OH1)	Original Braunvieh	*CNGB3*	0.099
BH14	Brown Swiss	*MRPL55*	0.032
OH6	Original Braunvieh	*LIG3*	0.039
HH13	Holstein	*KIR2DS1*	0.049
SH9	Simmental	*NUBPL*	0.043

Outlook

- Unsolved homozygous deficient haplotypes → need solving
- Phenotype validation:
  - Monitoring of risk-matings
  - non-embryonic lethal variants/haplotypes
- Inclusion in daily breeding practice → avoid futher risk-matings
- Similar reverse genetics screens can be performed in other (beef, local) populations with increasing SNP data availibity

Thank you very much!

Qualitas

Schweizerischer Nationalfonds

UNIVERSITÄT BERN

gcb Graduate School for Cellular and Biomedical Sciences

swissgenetics

ASR
Arbeitsgemeinschaft Schweizerischer Rinderzüchter
Communauté de travail des éleveurs bovins suisses

HOLSTEIN SWITZERLAND

SWISS herdbook SINCE 1890

BRAUNVIEH

Thank you for your attention!

Questions?