Stiftung Tierärztliche Hochschule Hannover
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# Exploiting genome data from bovine hospital cases to improve animal welfare on cattle farms

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# Background

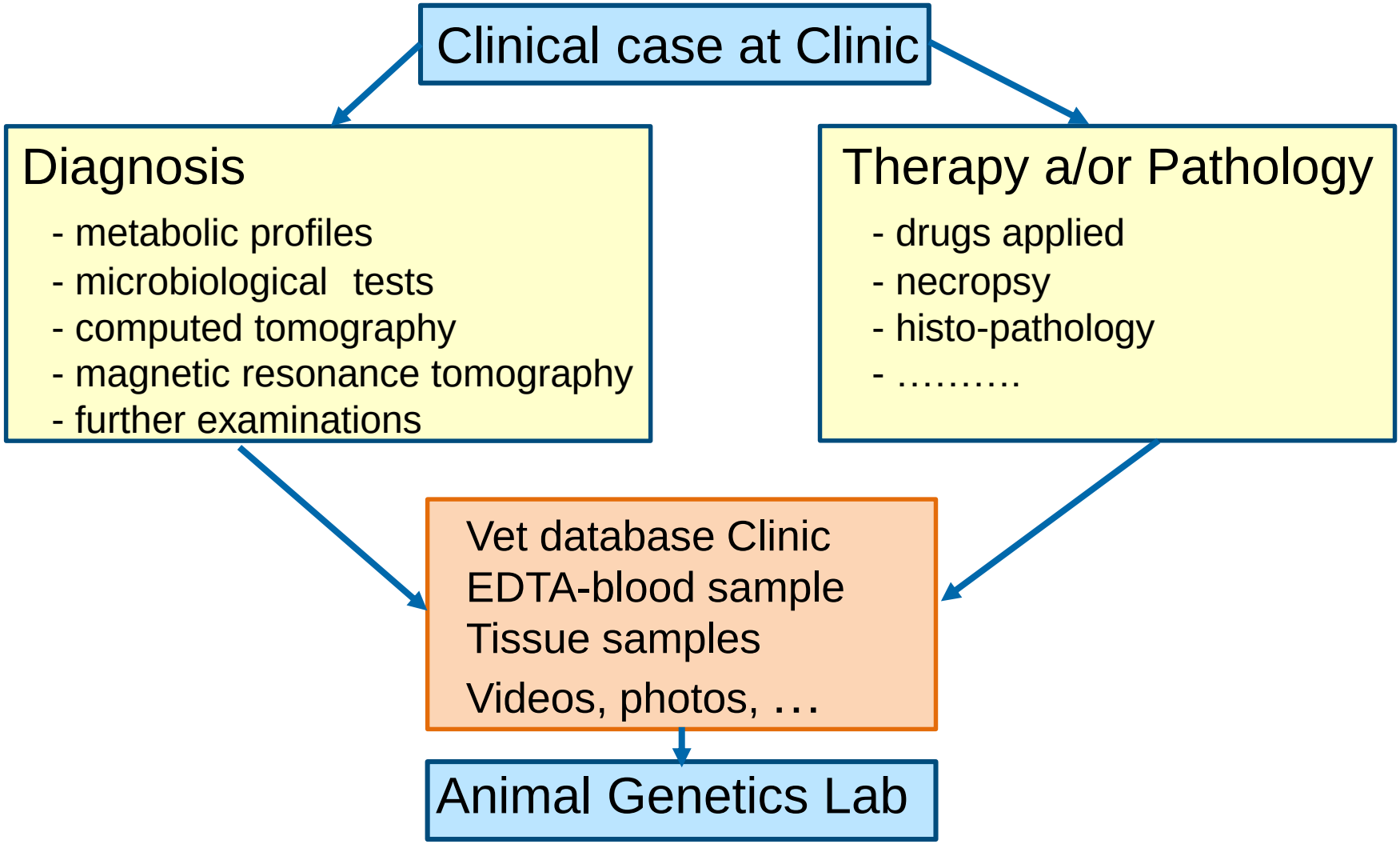
University Veterinary Clinic for Cattle in Hannover

- more than stationary 1000 patients per year
- many cases for surgery
- many cases for complicated diseases
- many cases with not yet known disease entities
- in addition, telephone calls from vets/farmers and requests on advice
- cases from herd health programs

Objectives

- use of these cases for genetic studies and extension services

# Materials and Methods



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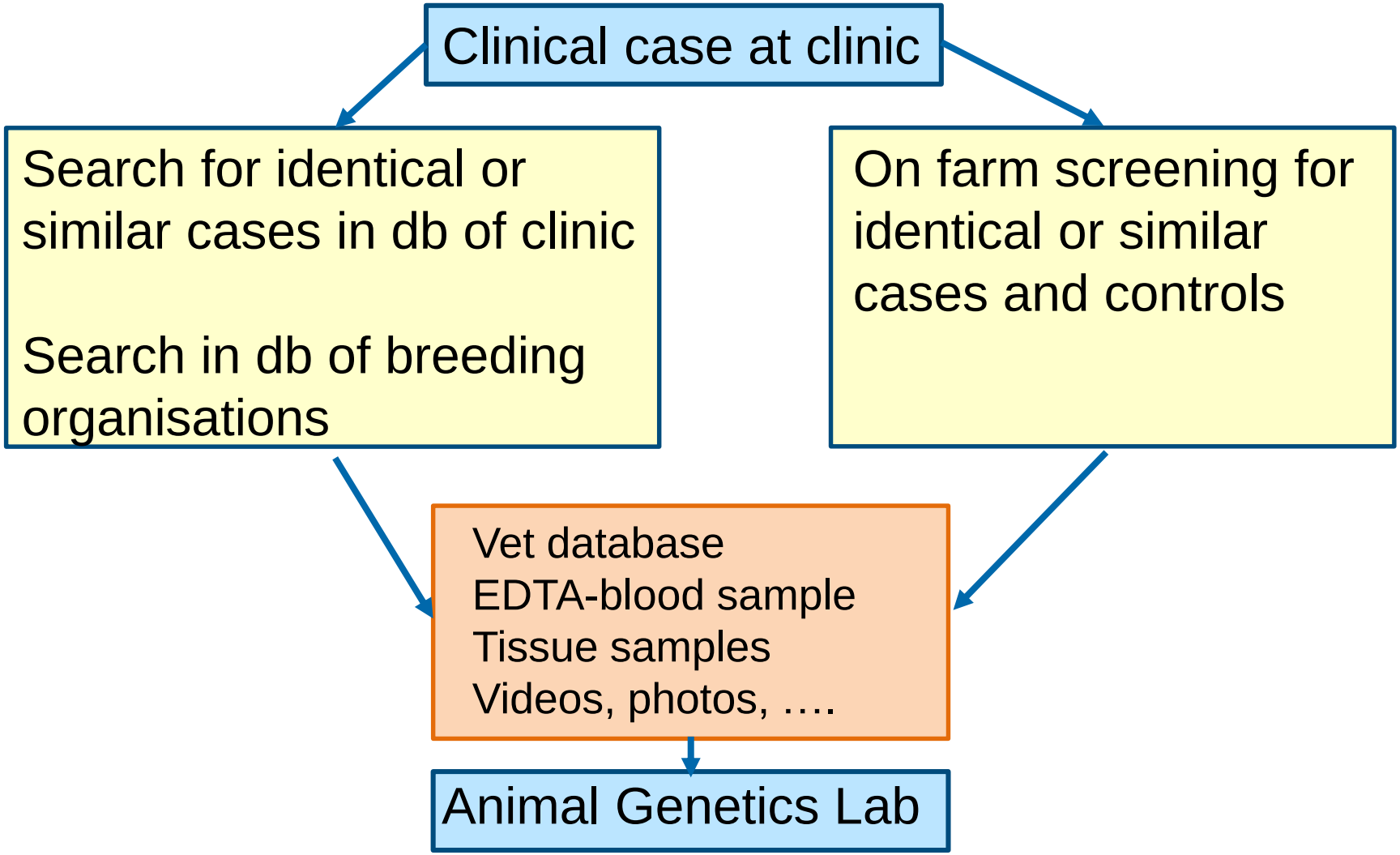
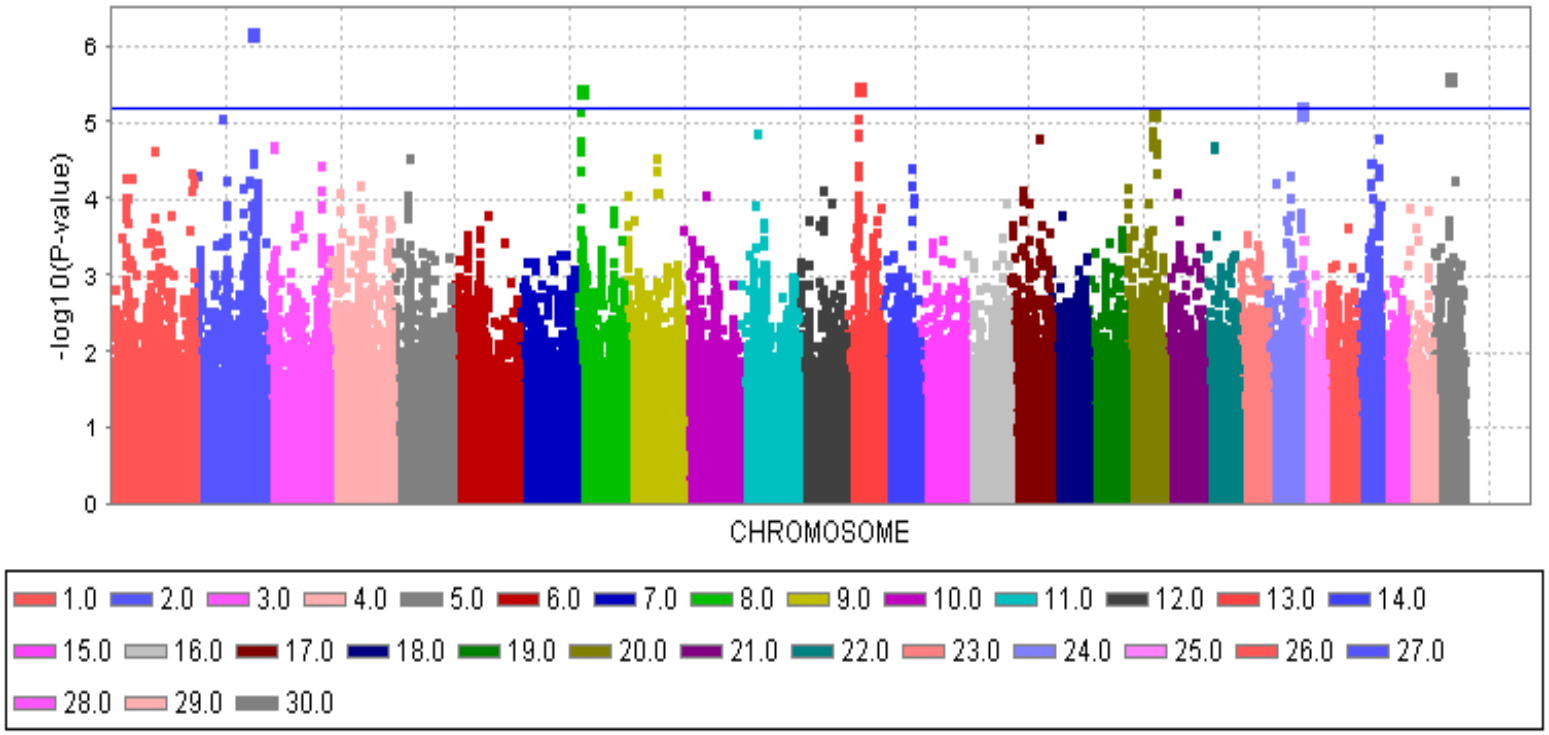


# Case Study – Left Displaced Abomasum

- Sampling started in 2006
- More than 6000 samples from clinical cases of displaced abomasum
- Mostly Holstein cows
- Heritability ~ 0.30 for LDA in Holsteins (GER)
- GWAS with 126 LDA-affected Holstein cows and 280 Holstein controls
- LDA cases represent 93 sires and controls 238 sires
- Controls > 5 lactations free from DA completed
- Illumina BovineHD BeadChip (588,554 SNPs in analysis)
- Validation in 1554 Holstein cows (1015 LDA cases and 539 controls)

# GWAS – Left Displaced Abomasum




Manhattan plot of the genome-wide association study for left-sided displacement of the abomasum (LDA) in German Holstein cattle using mixed linear model analysis

# Validation Study – Left Displaced Abomasum

| BTA | Position | MAF-cases | MAF-control | OR | $-\log_{10}$P-Genotype | $-\log_{10}$P-Allele |
|---|---|---|---|---|---|---|
| 2* | 94 | 0.06 | 0.22 | 4.3 | 36 | 38 |
| 2* | 120 | 0.07 | 0.14 | 2.3 | 11 | 10 |
| 8* | 6 | 0.33 | 0.24 | 1.6 | 6 | 6 |
| 13* | 60 | 0.36 | 0.43 | 1.3 | 10 | 4 |
| 19 | 59 | 0.22 | 0.16 | 1.4 | 3 | 3 |
| 27 | 32 | 0.04 | 0.11 | 3.3 | 14 | 17 |
| 27 | 43 | 0.33 | 0.40 | 1.4 | 10 | 4 |

# Case Study – Left Displaced Abomasum

BayesR
Marker heritability: 0.32
Number of SNPs in model: 2522

| Mixture components | No of SNPs | Proportion of SNPs | SNP-Variance | Relative SNP-variance |
|---|---|---|---|---|
| 1 | 586,032 | 99.571 | 0 | 0 |
| 2 | 2185 | 0.372 | 0.208 | 0.29 |
| 3 | 272 | 0.046 | 0.197 | 0.27 |
| 4 | 65 | 0.011 | 0.310 | 0.43 |

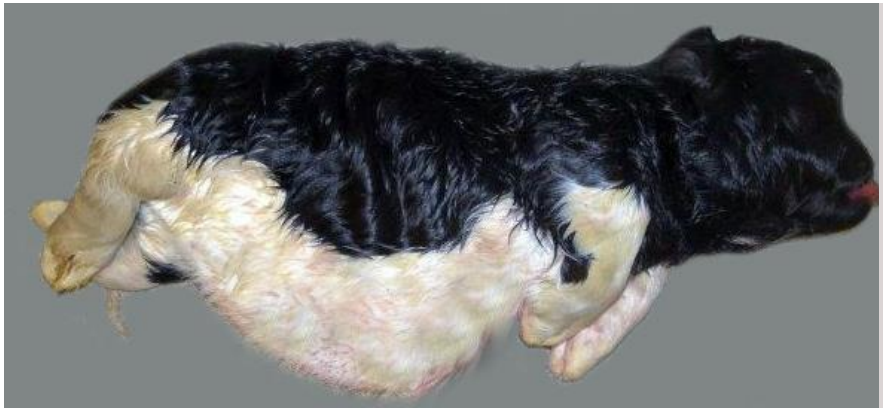
# BayesR– Left Displaced Abomasum

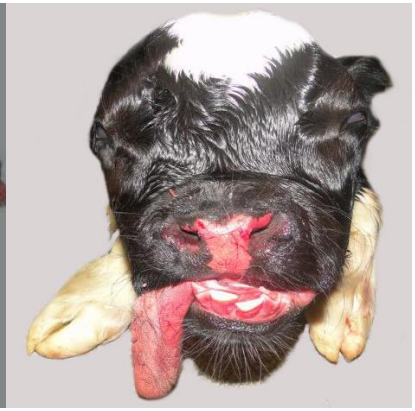
Location of the 65 mix-com-4 SNPs explaining highest proportion of LDA variance

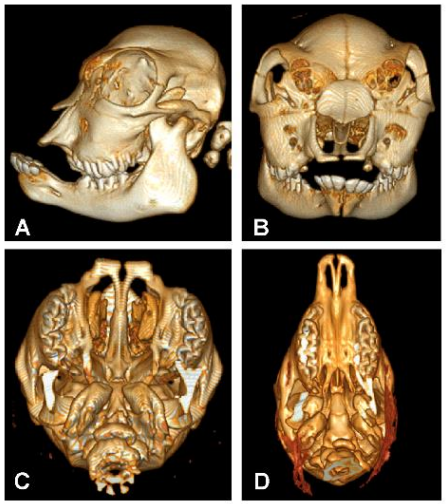
| BTA | Position | No SNPs | MAF | Beta | -log$_{10}$P-MLM |
|---|---|---|---|---|---|
| 1 | 157 | 4 | 0.44 | -0.28 | 4.3 |
| 2* | 120 | 13 | 0.16 | -0.17 | 6.2 |
| 8* | 6/80 | 5 | 0.37 | 0.06 | 5.5 |
| 11 | 30 | 6 | 0.28 | -0.38 | 4.9 |
| 13* | 60 | 6 | 0.32 | -0.34 | 5.5 |
| 17 | 25 | 3 | 0.49 | -0.06 | 4.8 |
| 22 | 17 | 3 | 0.09 | -0.25 | 4.7 |
| 27* | 32/43 | 8 | 0.47 | 0.15 | 4.8 |

# Case Study
# Lethal Chondrodysplasia (Bulldog-Syndrome)

- In total 3 cases with bulldog-syndrome in a herd
- Parents normal
- All cases paternal half-siblings
- Bulldog-syndrome not yet observed in this herd
- Dams and sire of cases not related







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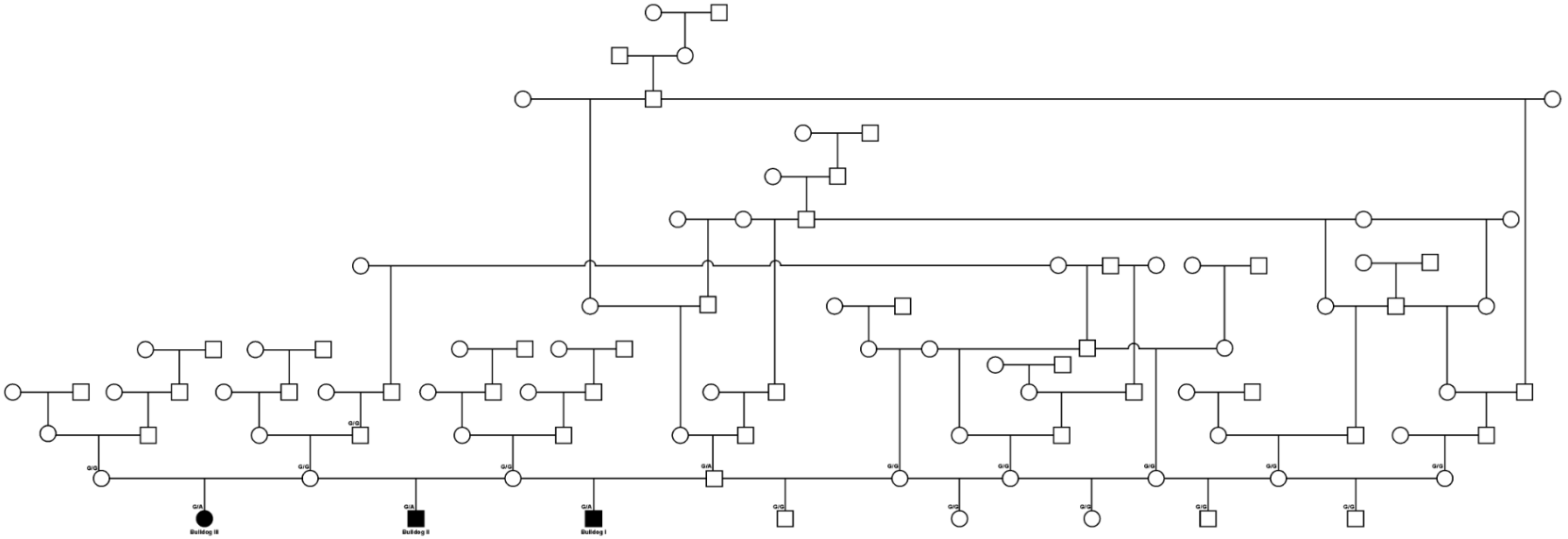

Sampling of cases and controls including parents, siblings and distantly related animals

Recessive inheritance unlikely
Germline mutation on an autosome with dominant effect likely
Sire of cases may be suspected as source due to familiarity and identical signs in all cases

# Case Study
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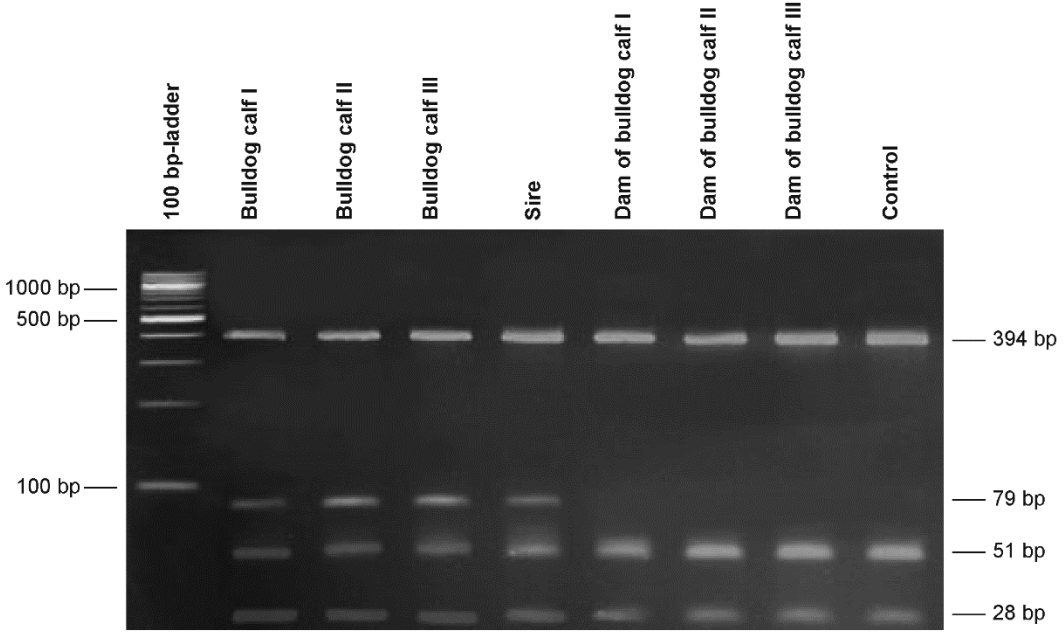
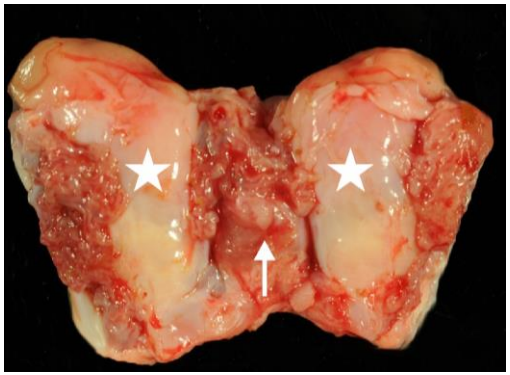



- Search of whole genome sequencing data of a case, normal half-sib and sperm of the sire
- Validation of the *COL2A1*. g.32476082G>A (ss2019324576) mutation in sperm of the sire and all cases
- Validation of wildtype in all dams and a large cohort of control samples

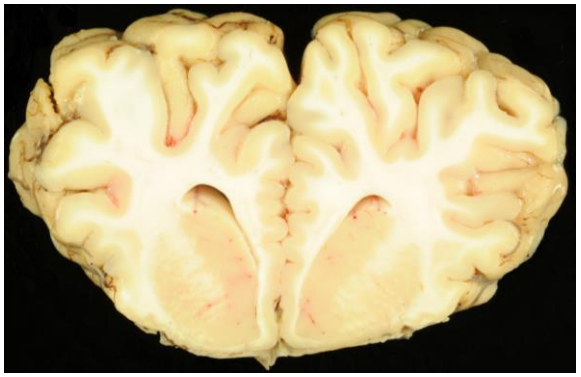
# Case Study
# Duplication of the Pituitary Gland Syndrome

- First description of DPG-plus syndrome in cattle
- Case: Crossbred calf from German Brown cow and Belgian Blue-White sire
- Twin with a normal co-twin
- DPG-plus Syndrome includes duplication of hypophysis, agenesia of corpus callosum, median cleft lip and jaw, cleft palate

Median cleft lip



Duplication of hypophysis

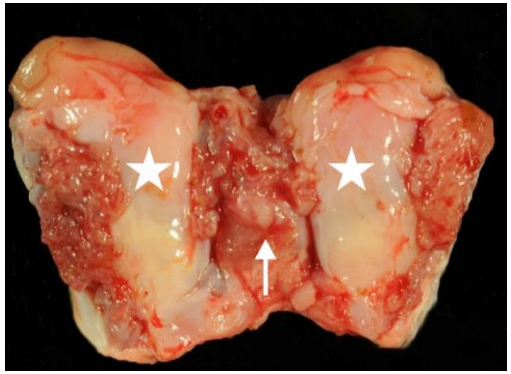


Missing corpus callosum

# Case Study
# Duplication of the Pituitary Gland Syndrome

- Not yet reported in cattle
- Further cases not identified
- Whole Genome Sequencing of the case and dam
- Recessive mutation ruled out
- Heterozygous dominant maternal germline or embryonic mutation likely
- Paternal germline mutation less likely

Median cleft lip



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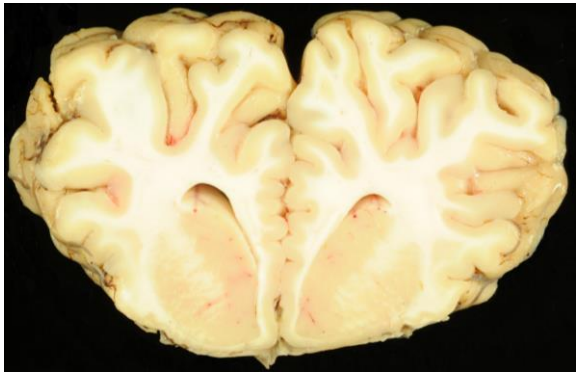

Missing corpos callosum

# Conclusions

- Cases from veterinary clinic valuable resource for research
- Complex diseases with economical impact (surgery, severe cases)
- Access to rare diseases and congenital anomalies
- Next generation sequencing an essential tool
- Increased demand from farmers and breeders for genetic tests
- Further improvements of the workflow possible
- Consortium at University of Veterinary Medicine including all specialists
- Open for co-operation with other groups and individual researchers

# Thank you for your attention!