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Homozygosity mapping of a Weaver-like disorder in Tyrol Grey cattle

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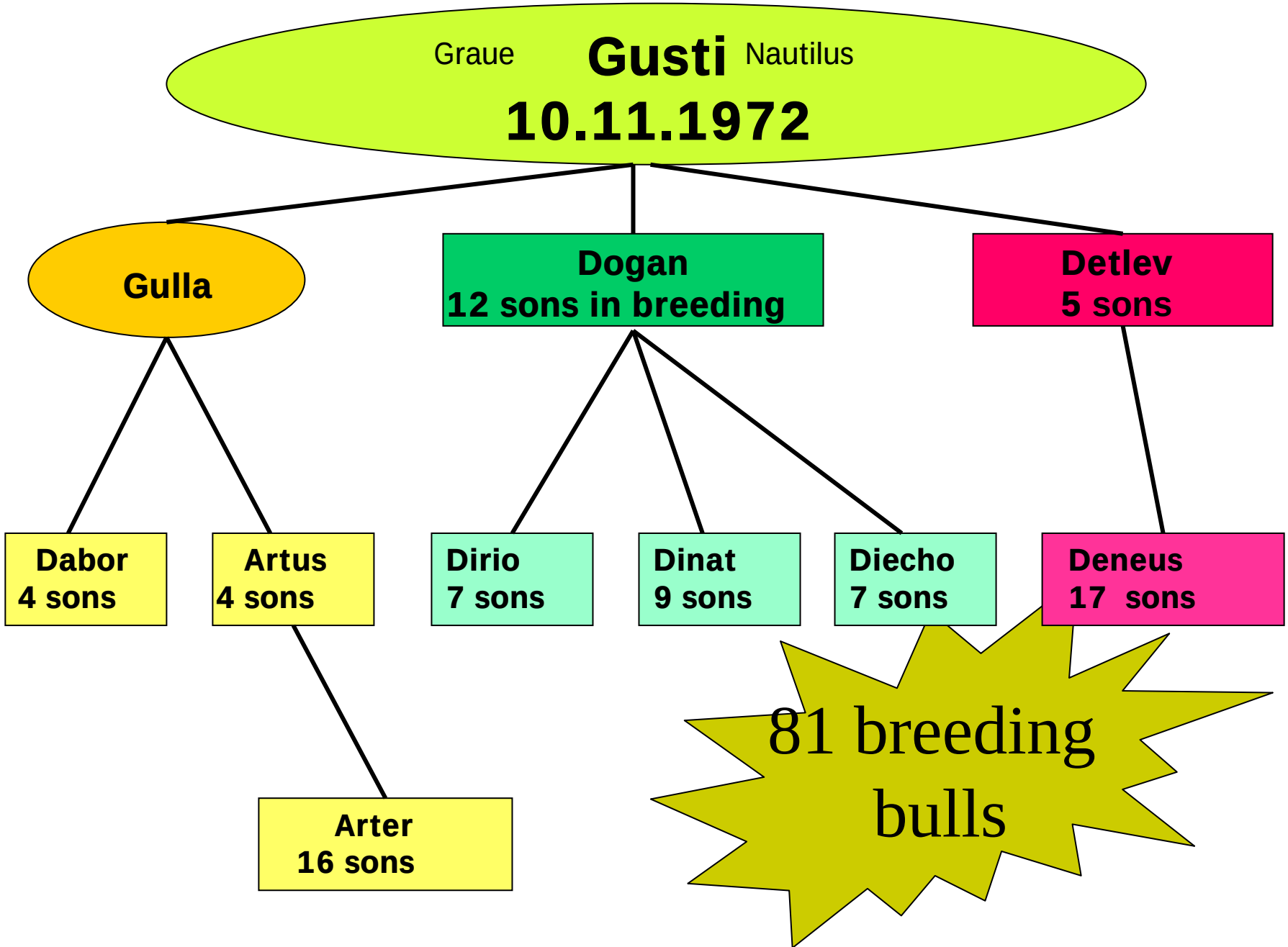
The disorder

- First observed in 2003
- Calves lose control over the nervous system of the hind part of the body at 3-5 months of age
- “Dream dancer”
- Very similar to Weaver in Brown Swiss
  - Weaver occurs much later in life
  - Locus was excluded by testing
- 31 cases by mid 2008

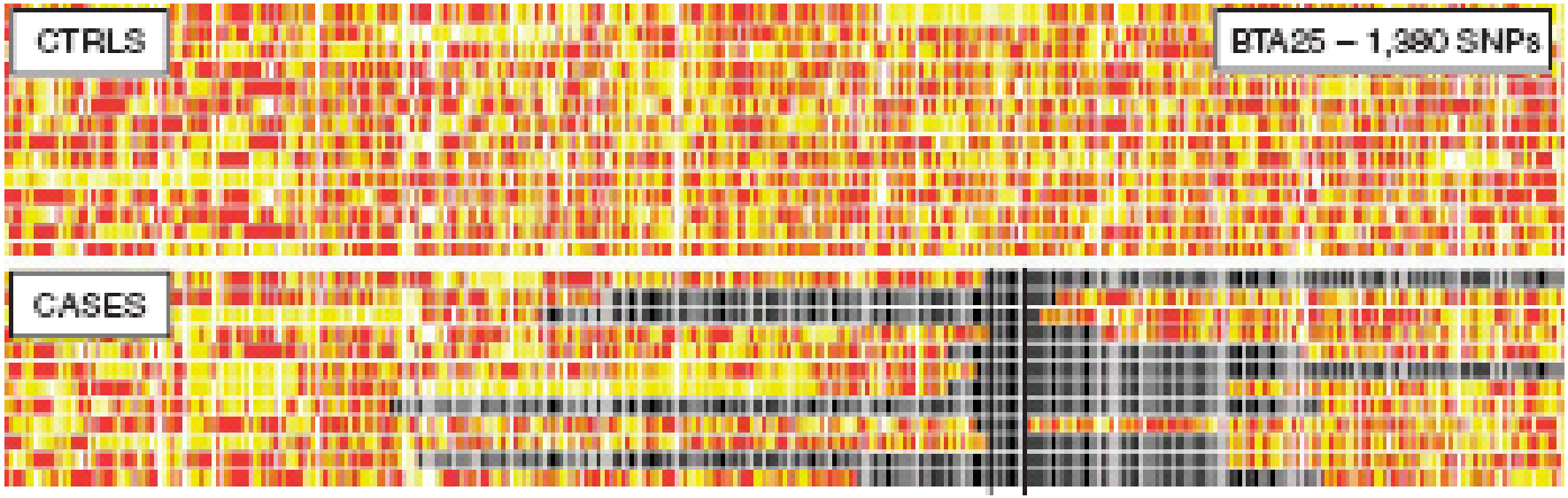

Graue
Gusti
Nautilus
10.11.1972
Gulla
Dogan
12 sons in breeding
Detlev
5 sons
Dabor
4 sons
Artus
4 sons
Dirio
7 sons
Dinat
9 sons
Diecho
7 sons
Deneus
17 sons
Arter
16 sons
81 breeding bulls

First steps

- Meeting in April 2008
- Decided to genotype cases, carriers and some unrelated animals with the Illumina 50k SNP chip
  - 15 cases
  - 15 parents of other cases
  - 8 animals not related to Gusti
  - 21 potential carriers
- Genotypes available Sep 23, 2008

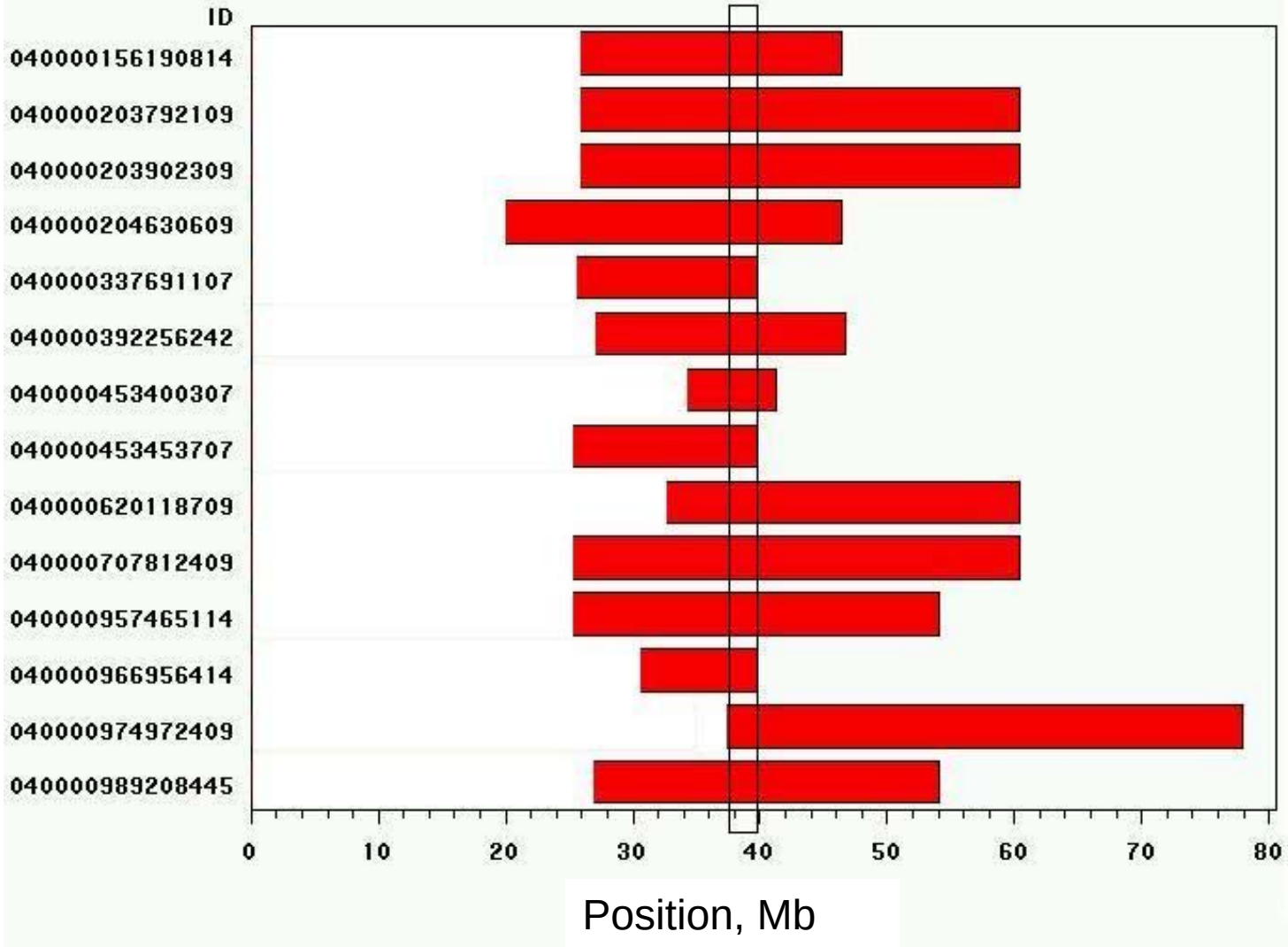
Homozygosity mapping

- Search for a region of the genome that is homozygous and identical for all cases



Charlier et al, June 2008

Chromosome 16



Chromosome 16

- 77.87 Mb, 1606 SNP
- Polymorphic: 1304
- Homozygous region:
  - SNP 719 – 765
  - Mb 36.88 – 39.75
- Reference haplotype: B A B B A B A B B A B B B A A B A A B B B A A A B A B A B B A B B B B B B A A A B A A B B

Carriers

- Check for compatibility with reference haplotype at SNPs 719-765
- Two carriers with shorter compatible region
  - one is not compatible at positions 723-725
  - one is not compatible at positions 730 and 737
- This narrows the candidate region to SNP 738–764: Mb 38.33-39.61

Development of a marker test

- 10 of the 21 “test” animals for which the SNP chip genotyping was performed are suspected carriers
- Use of 4 microsatellite markers in the region. Confirmed all cases and carriers
- Offered for routine testing from Dec 2008

Search for causative mutation

- Three candidate genes, with function related to nervous system
  - ***MFN2*** **19 Exons**
  - ***MTHFR*** **12 Exons**
  - ***TARDBP*** **6 Exons**
- Sequencing of exons did not uncover a potentially causative mutation

Search for causative mutation

- Sequencing of less suspicious genes in the area
- Potentially causative mutation found !!!
- Synonymous mutation
  - Callipyge like
- Many more cases, carriers and unrelated animals genotyped, no conflict

Search for causative mutation

- Living case recovered in June 2009
- Many tests under way to confirm the function of the potentially causative mutation

Conclusion

- Extremely quick development of a marker test
  - 7 months from decision to search for the genomic region to availability of a routine test
- 5 days of programming work to develop the procedures and find the region
  - longwide.f95, homomap.f95, homochunks16.f95, checkcarrier.f95
- Use of carriers may prove useful to refine the candidate region

Conclusion

- Frequency of the allele in the population is high (>10% carriers)
- Tyrol Grey assoc. is to decide whether to lift the ban carriers from breeding for particular matings

Detective work of Cord Drögemüller; Current state

Dollar