Decoding the functions of Mendelian traits in domestic animals

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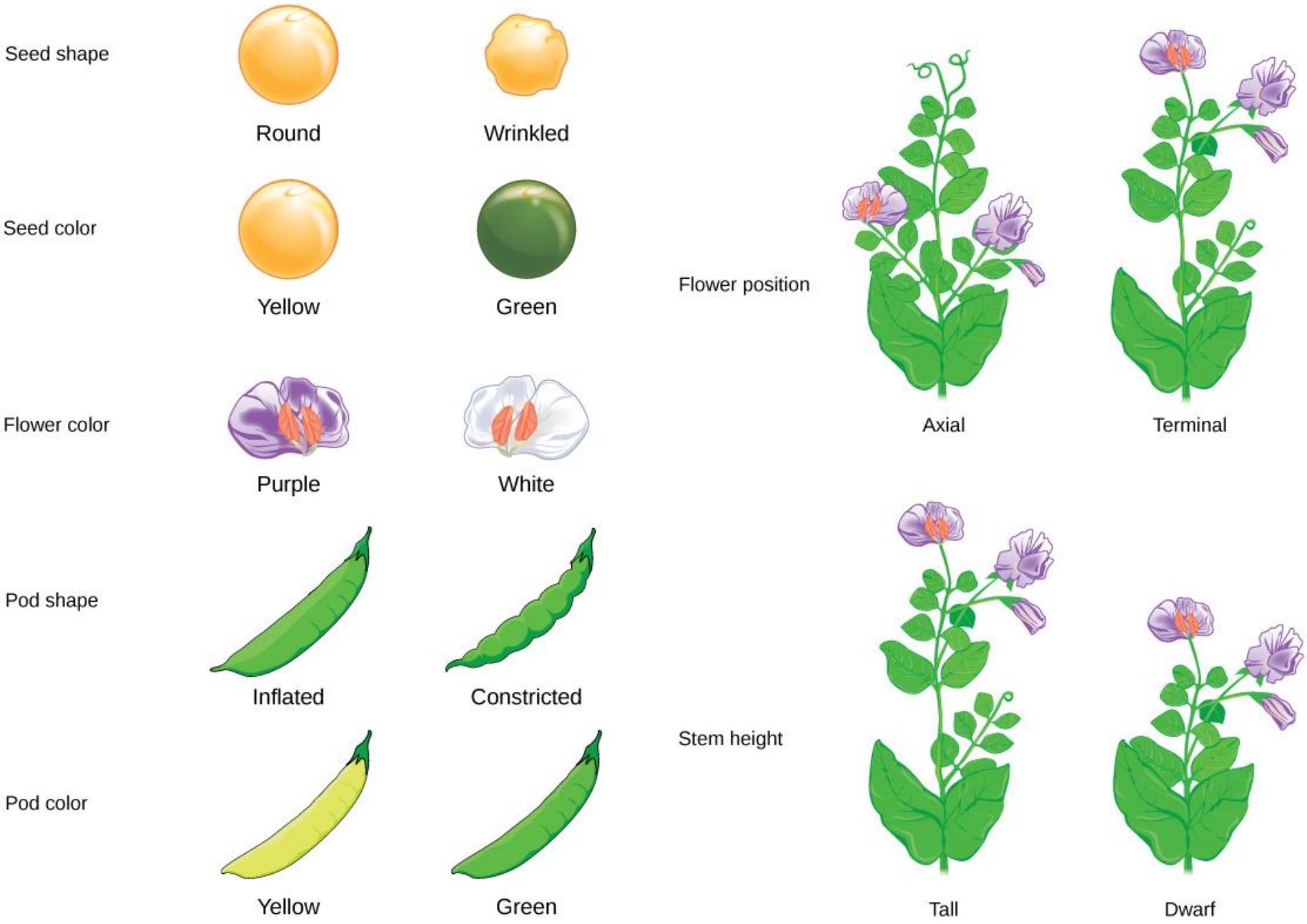
1865, Brünn/Brno

- Mendel presented the results of his research at sessions of the Nature Research Society of Brünn on Feb. 8 and March 8, 1865.
- Based on experiments with >28,000 pea plants
- Introduced the concepts of dominant and recessive "factors"


Seed shape
Round
Wrinkled
Seed color
Yellow
Green
Flower color
Purple
White
Pod shape
Inflated
Constricted
Pod color
Yellow
Green
Flower position
Axial
Terminal
Stem height
Tall
Dwarf

1865, Brünn/Brno

Two laws of heredity:

1) **The Law of Segregation**. Even though an organism inherits two factors from its parents, it contributes only one of them to its offspring.
2) **The Law of Independent Assortment.** The factors for different traits are sorted separately from one another.

Mendelian inheritance, Mendelian traits

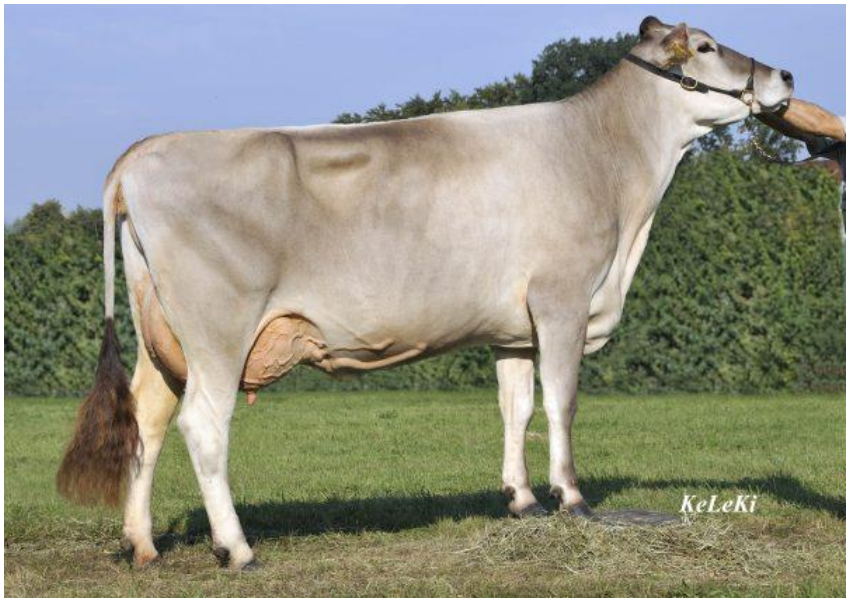
Mendelian traits in livestock

- Example traits
  - Coat color and color distribution
  - Recessive disorders
  - SLICK phenotype in cattle

- Decoding of gene functions

Mendelian traits in livestock

- Basic body color
  - White, grey, fawn, red, brown, black, …
  - Black is dominant over red/brown
    - Many other Mendelian patterns are well known, using Mendel‘s strategy of targeted mating of particular types, and subsequent counting
- Coat color pattern
  - Monochrome, spotted, sprinkled, white-head, …
  - Uni-colored is dominant over spotted



X

X

↓

Finding the Grey mutation in horse

- Hroses are born in base color - black, bay, chestnut, ..
- Grey mutation: early greying of hair
- Mutation is dominant: one copy is enough to make horses greying

Lipizzaner project

Measured level of grey with a Chromometer

L*=34

L*=43

L*=52

L*=63

L*=68

L*=72

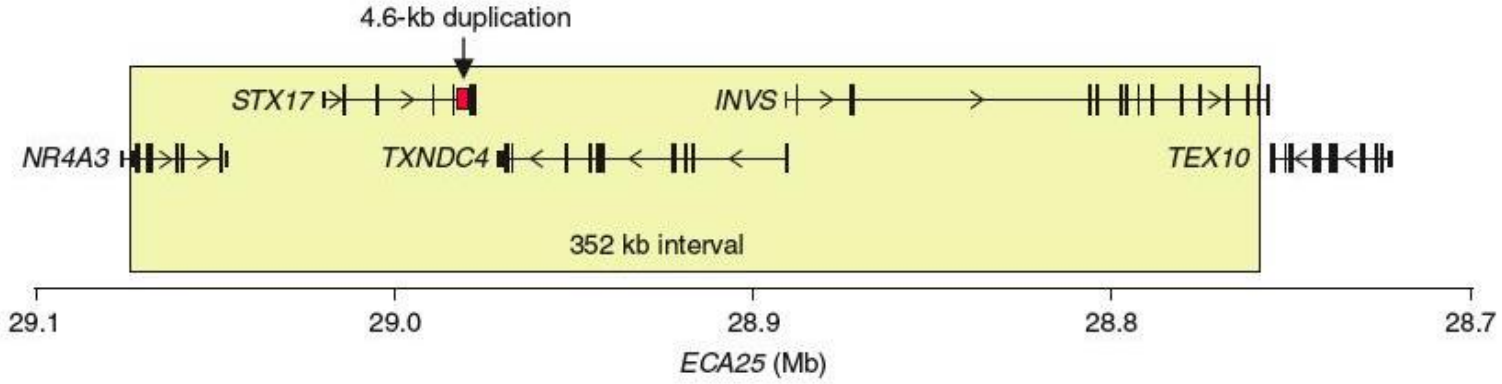
L*=77

Recorded phenotypes of melanoma, vitiligo, speckling

National studs in AT, SLO, SLK, HU, CRO

Causative mutation

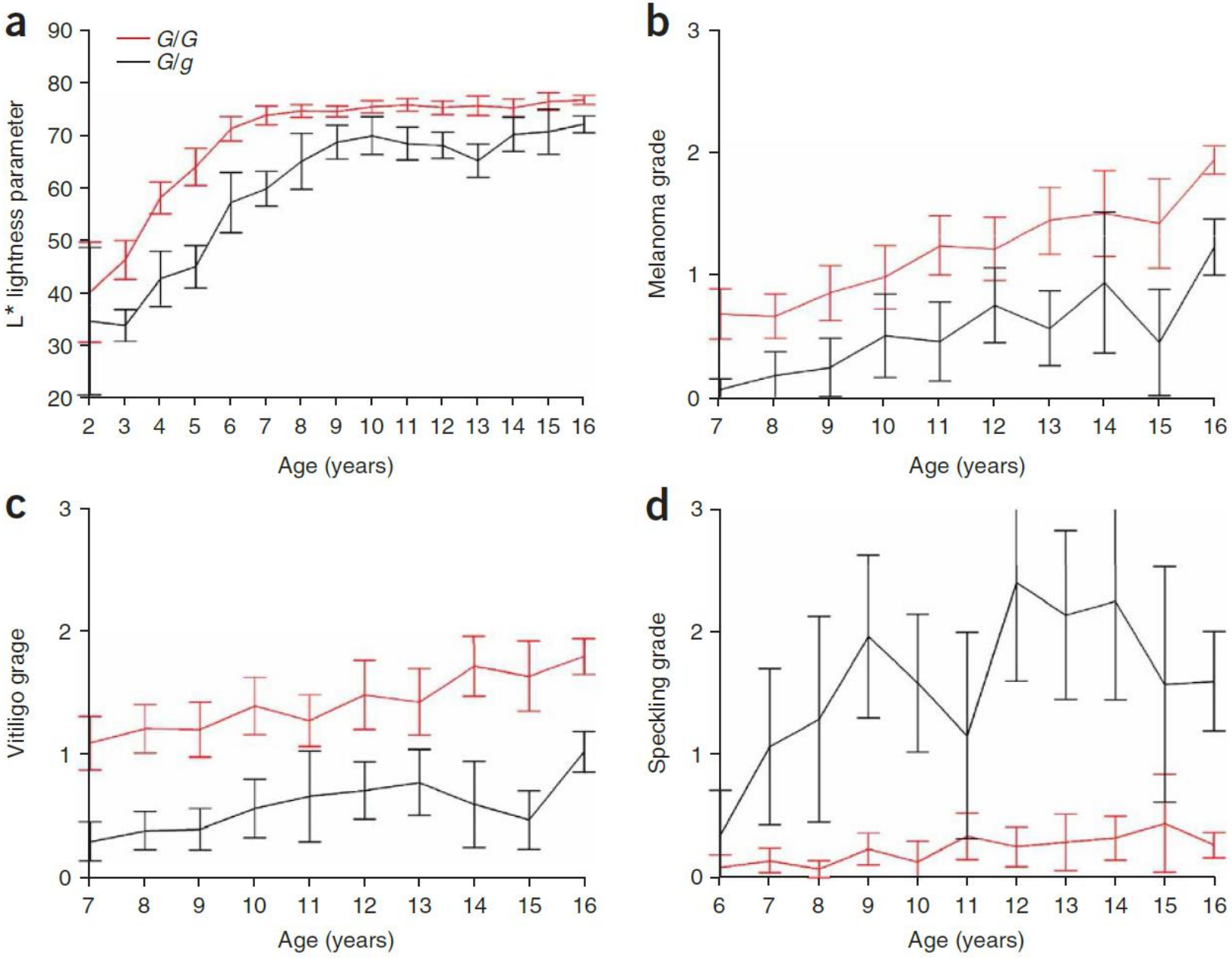
- Group of Leif Andersson, Uppsala
- Duplication of an intron of the gene STX17, 4,600 bases long



- Regulatory mutation, non-coding region

Effects of the mutation

- Homozygous greys, carrying two copies of the mutation
  - Greying is much faster
  - Have melanoma more frequently
  - Are almost never speckled


a
G/G
G/g
L* lightness parameter
90
80
70
60
50
40
30
20
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Age (years)
b
Melanoma grade
3
2
1
0
7 8 9 10 11 12 13 14 15 16
Age (years)
c
Vitiligo grage
3
2
1
0
7 8 9 10 11 12 13 14 15 16
Age (years)
d
Speckling grade
3
2
1
0
6 7 8 9 10 11 12 13 14 15 16
Age (years)

Color-sidedness of coat in cattle

Search for causative mutation

- Groups of Michel Georges und Tosso Leeb
- Candidate:
  - KIT – responsibe for color patterning in many animal species
- Mutation:
  - Duplication of a part of KIT, translocation onto a different chromosome

Serial Translocation with circular intermediates (dominant)

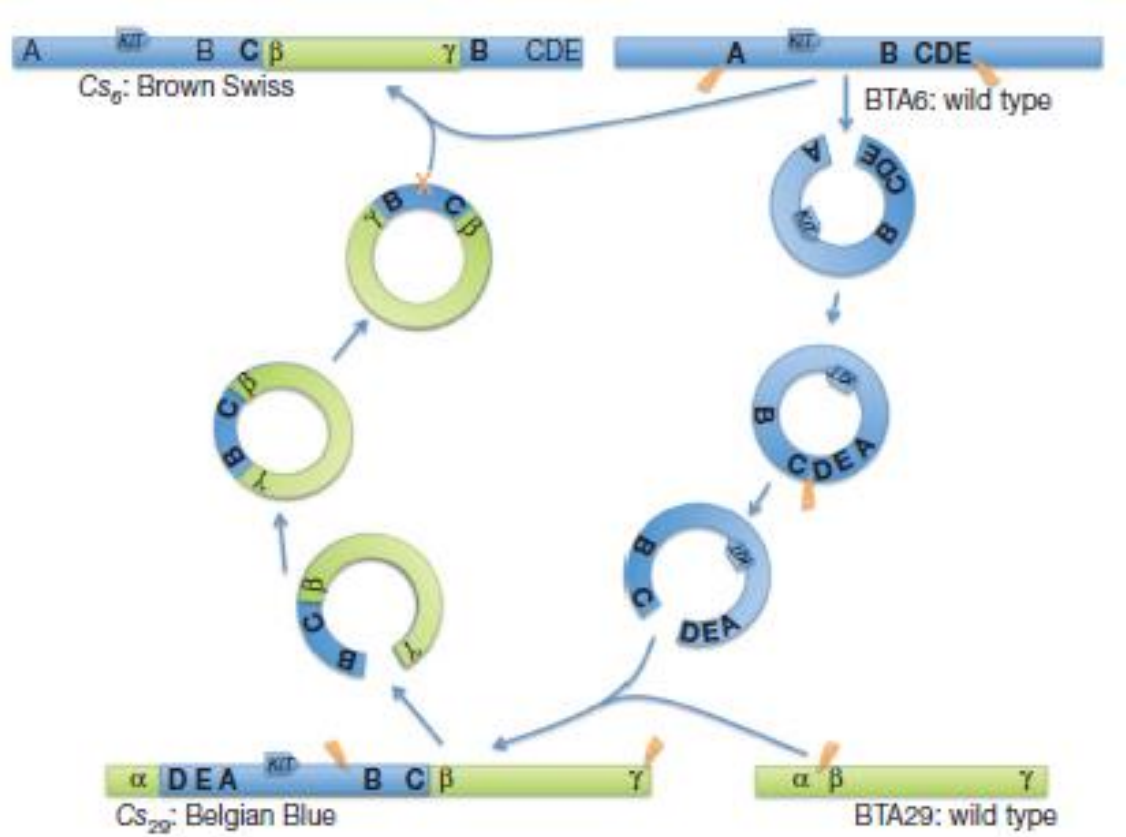


Figure 3 | Model for the generation of the colour-sided Cs_{29} and Cs_6 alleles by serial translocation via circular shuttling intermediates.

Pattern of inheritance not observed before!

nature genetics

A *cis*-acting regulatory mutation causes premature hair graying and susceptibility to melanoma in the horse

Gerli Rosengren Pielberg[1], Anna Golovko[1,12], Elisabeth Sundström[2,12], Ino Curik[3], Johan Lennartsson[4], Monika H Seltenhammer[5], Thomas Druml[6], Matthew Binns[7], Carolyn Fitzsimmons[1], Gabriella Lindgren[2], Kaj Sandberg[2], Roswitha Baumung[6], Monika Vetterlein[8], Sara Strömberg[9], Manfred Grabherr[10], Claire Wade[10,11], Kerstin Lindblad-Toh[1,10], Fredrik Pontén[9], Carl-Henrik Heldin[4], Johann Sölkner[6] & Leif Andersson[1,2]

LETTER

doi:10.1038/nature10757

Serial translocation by means of circular intermediates underlies colour sidedness in cattle

Keith Durkin[1], Wouter Coppieters[1], Cord Drögemüller[2], Naima Ahariz[1], Nadine Cambisano[1], Tom Druet[1], Corinne Fasquelle[1], Aynalem Haile[3], Petr Horin[4], Lusheng Huang[5], Yohichiro Kamatani[6], Latifa Karim[1], Mark Lathrop[6], Simon Moser[7], Kor Oldenbroek[8], Stefan Rieder[7], Arnaud Sartelet[1], Johann Sölkner[9], Hans Stålhammar[10], Diana Zelenika[6], Zhiyan Zhang[1], Tosso Leeb[2], Michel Georges[1] & Carole Charlier[1]

ANIMAL GENETICS Immunogenetics, Molecular Genetics and Functional Genomics

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A complex structural variant at the *KIT* locus in cattle with the Pinzgauer spotting pattern

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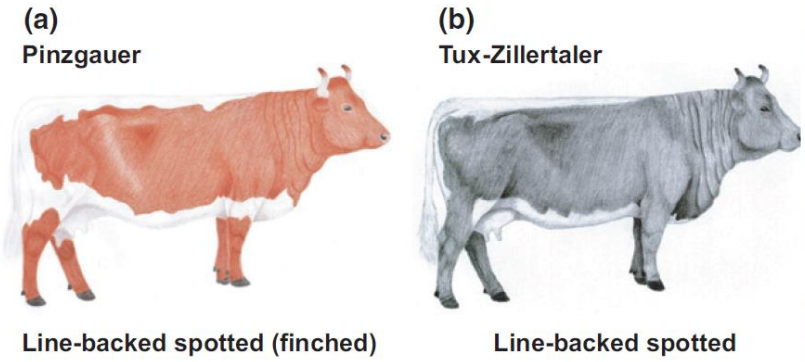


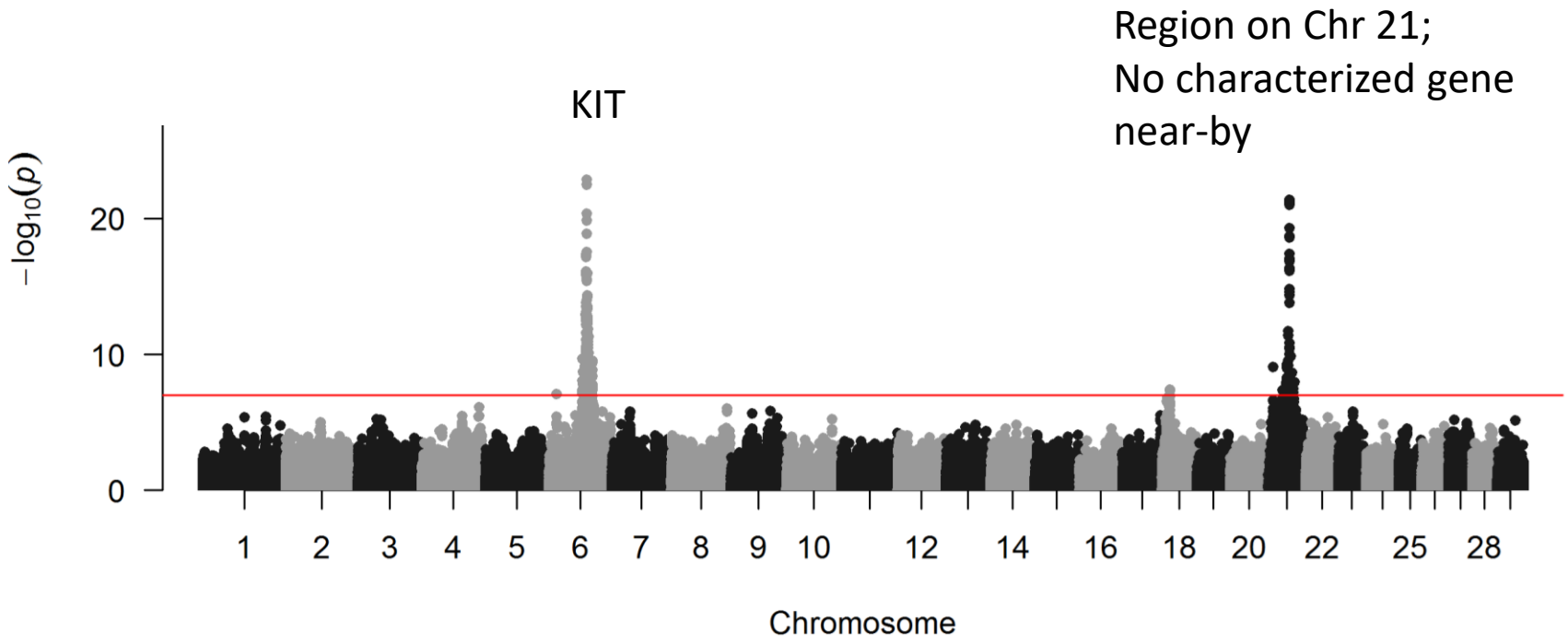
Figure 1 (a) Coat colour phenotype of a typical Pinzgauer cow. (b) So

Color patterns of Gir cattle in Brazil

monochrome

speckled

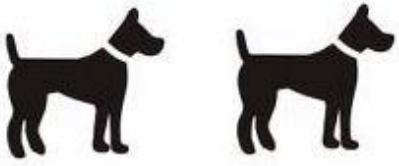
Genome wide association study: monochrome vs. speckled

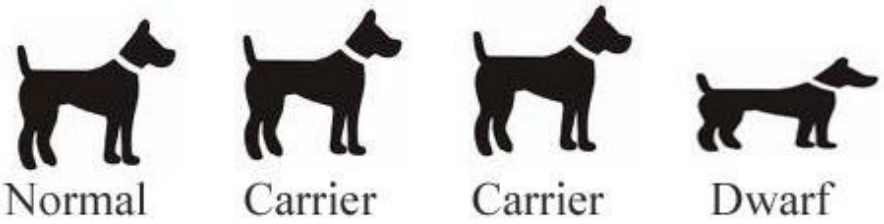


Recessive Disorders

- A plague for breeders of livestock and other deomestic animals
  - Very small effective population size (~30-300)
  - Big chance to get identical chuncks of chomosomes transmitted for both parents
    - Common ancestor not many generations ago
  - If the common ancestor is heterozygous carrier of a recessive disorder:

    -> Chance of homozygoty


Carrier
Carrier

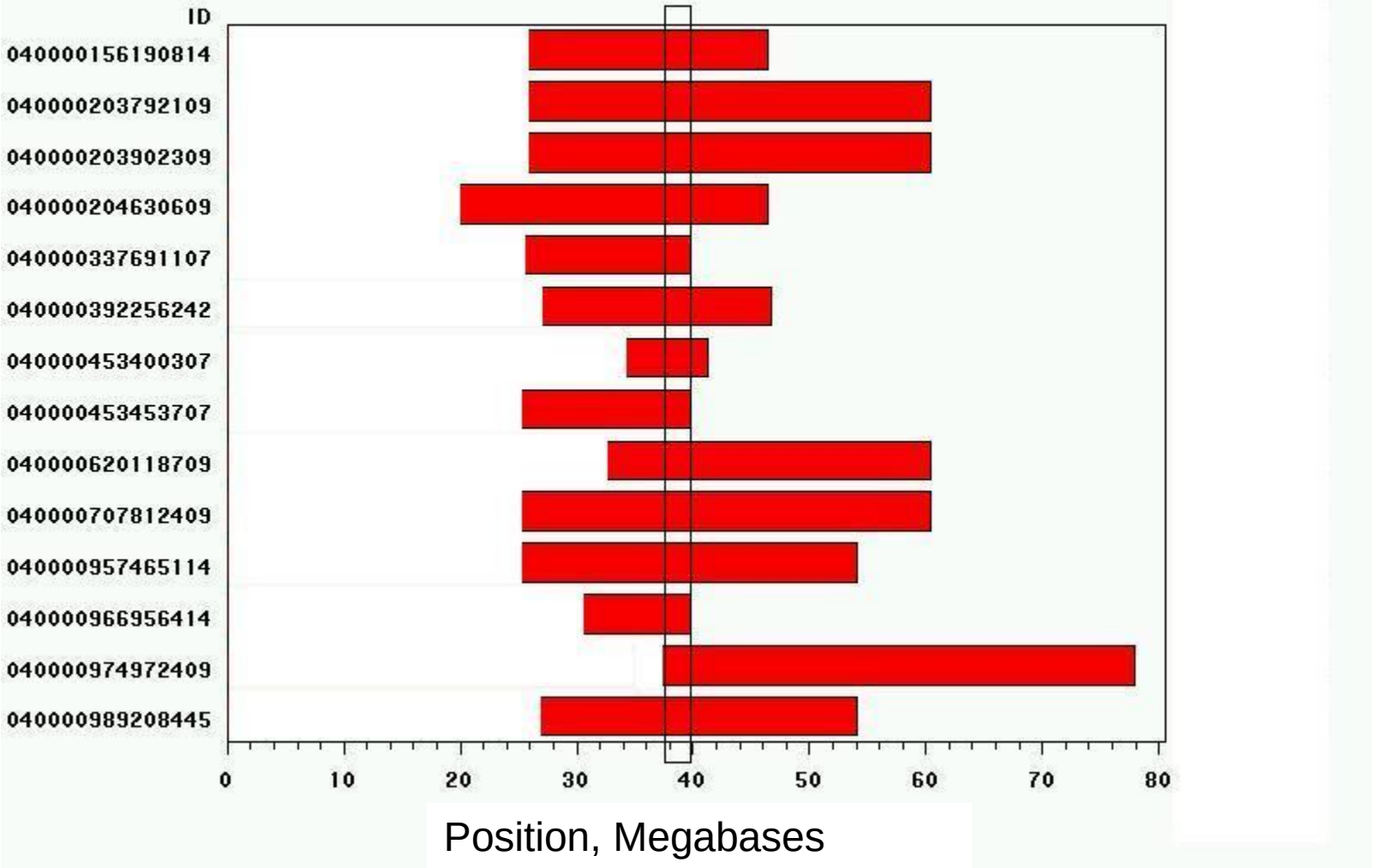

Normal
Carrier
Carrier
Dwarf

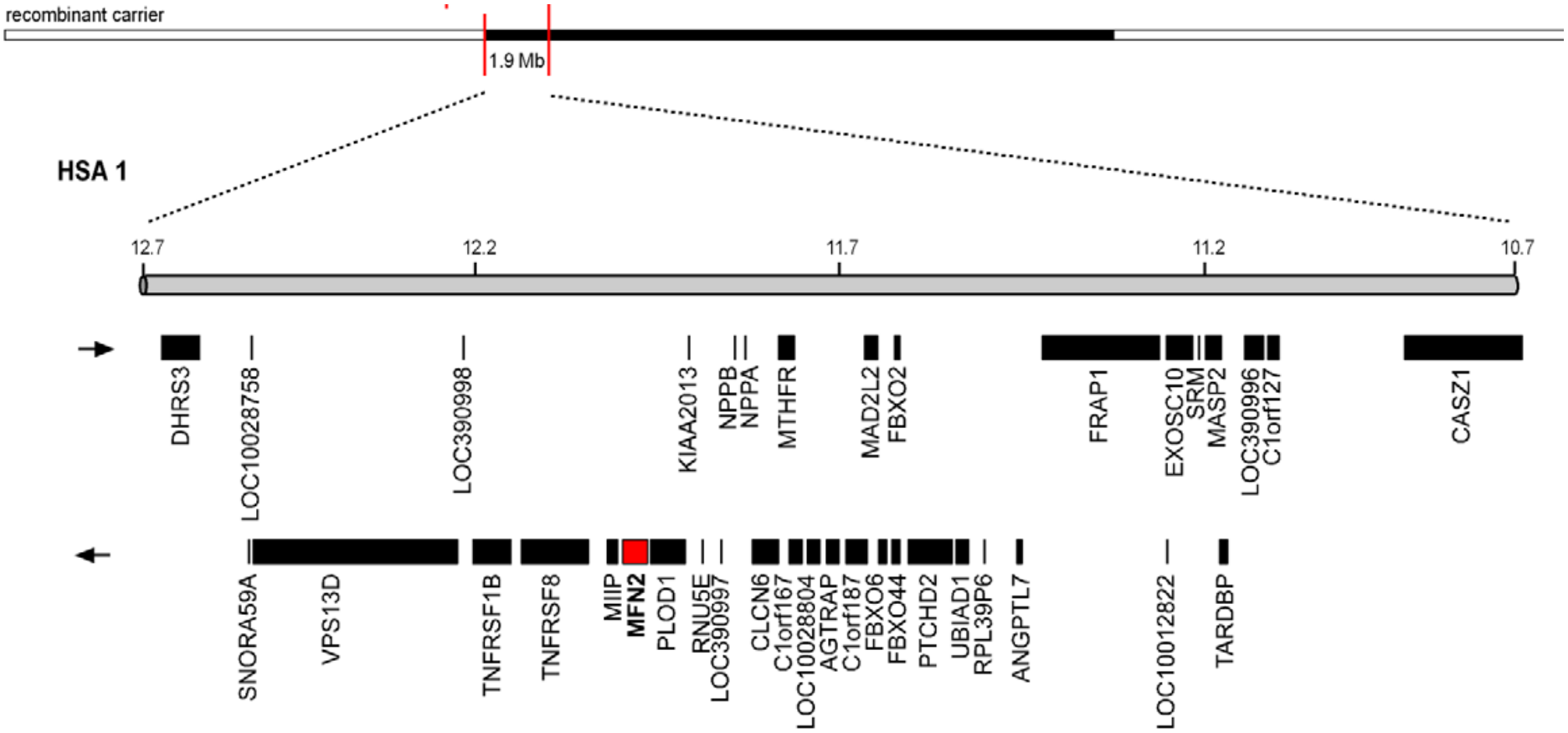
Rezcessive disorder in Tyrol Grey cattle

- First observed in 2003
- Demetz-Syndrome
- Symptoms:
  - Observed in calves, ~3 Mo. old
  - Nervous syndrome

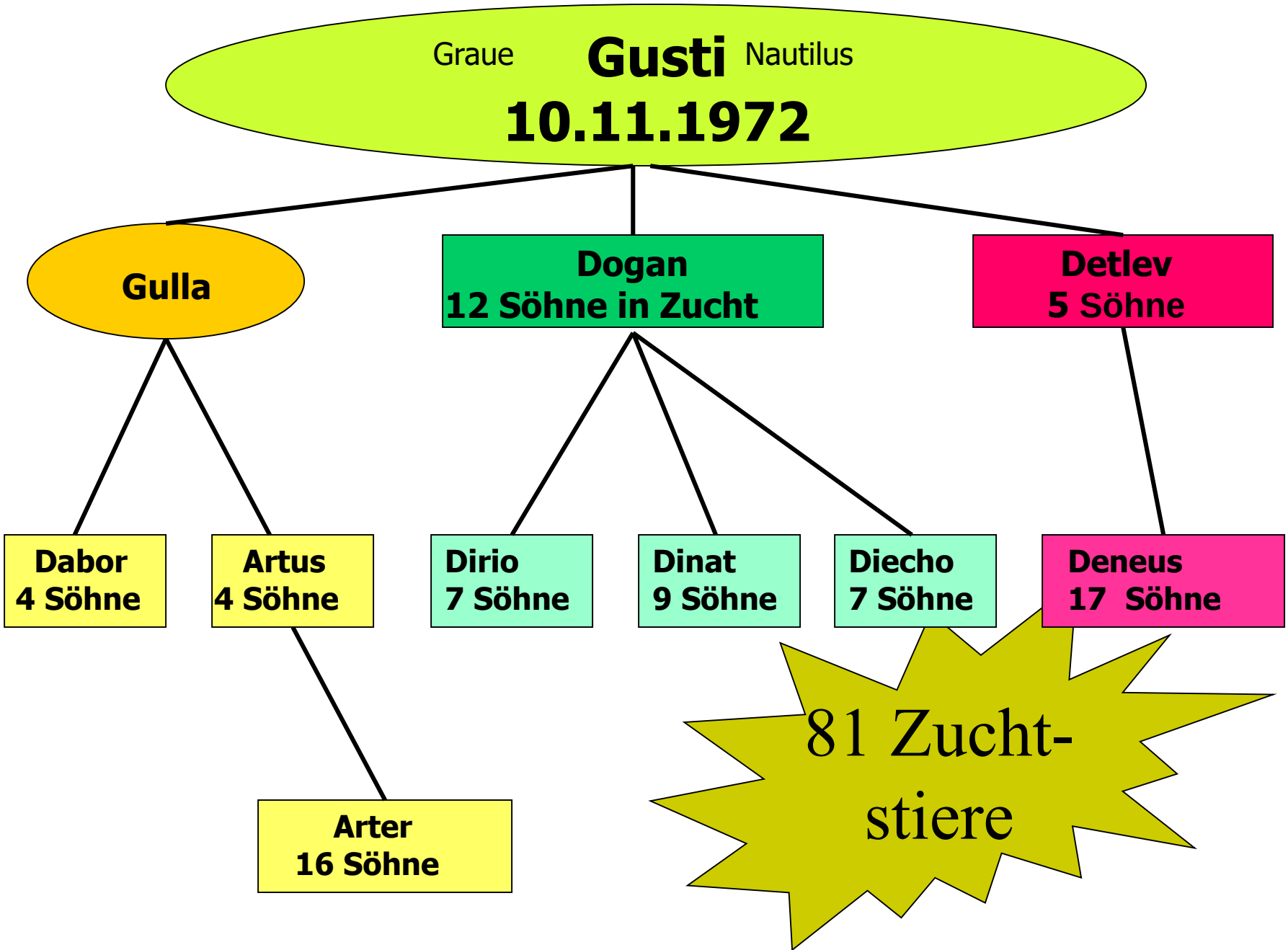
- Gusti (*1972) is in the pedigree of all diseased animals
- Genotyping of deseased animals, homozygoty mapping

Region on chromosome 16, all diseased animals with homozygous segments





- Mutation found in MFN2 gene
  - Mutations of MFN2 case a recessive disorde in humans: Marie-Charcot-Tooth disease
- Mutation is synonymous, but regulatory!


Graue
Gusti
Nautilus
10.11.1972
Gulla
Dogan
12 Söhne in Zucht
Detlev
5 Söhne
Dabor
4 Söhne
Artus
4 Söhne
Dirio
7 Söhne
Dinat
9 Söhne
Diecho
7 Söhne
Deneus
17 Söhne
Arter
16 Söhne
81 Zucht-
stiere

Management of genetic disorders

- Very simple, if mutation is known!
- Cheap genotyping of the causative variant(s)

  -> Exclude carriers from breeding

  -> Or: avoid mating of carriers

SLICK

My favorite Mendelian trait

- Dominant variant of the Prolactin Receptor (PRLR) gene
- Having a single copy of such a variant makes cattle heat tolerant / thermotolerant
  - Shorter hair and lower follicle density across the coat than wild type animals
  - Body temperature under heat stress lower than normal
  - Sweating rate higher under such conditions
- Productivity (milk production + fertility) under heat stress is higher

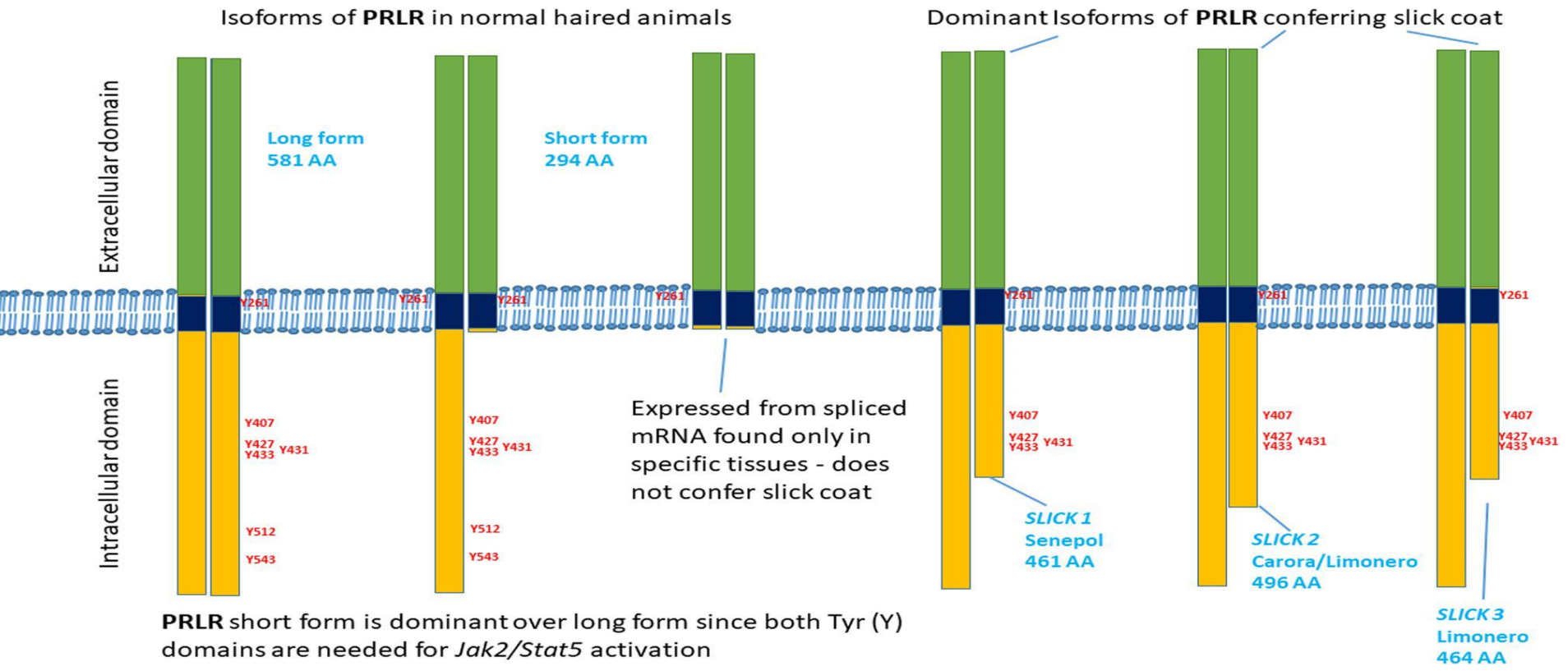
10568
10568

The **SLICK** phenotype

- The SLICK phenotype was originally found in Senepol cattle
  - Criollo type taurine catte of the Carribean
- Heat tolerance of the dominant Senepol variant was apparent to USDA researchers 30 years ago
  - Intogression of the variant into Holstein Friesian in Florida by repeated backcrossing
  - Get rid of most of the Senepol genome except for the beneficial PRLR variant
  - Develop a SLICK Holstein Friesian

The genetic mechanism causing **SLICK**

- Several mutations found,Mechnism is the same, causing shortening of the prolactin receptor, operating at the cell wall



Gene editing for SLICK phenotype

- SLICK animals have been successfully produced via gene editing
  - AceliGen Inc. (subsidiary of Recominetics Inc.)
- TALEN and Crispr-CAS technologies

Bill & Melinda Gates Foundation project

- Precision Crossbreeding of African Dairy Production Systems
- https://www.prnewswire.com/news-releases/acceligen-launches-program-for-precision-crossbreeding-of-african-dairy-production-systems-301137450.html
- Crosses of Holstein Friesian x Gir
  - Gene edited for SLICK and several health related (Trypanosomis, brucellosis,…) candidate variants
- To be crossbred with local breeds in Africa

Gene editing or backcrossing?

- Introduction of the SLICK variant into cattle populations in the tropics
- Note: SLICK exists in particular cattle populations anyway
- Is gene editing a safe technology ??
  - I think it is !
- Yet, not many gene edited SLICK animals are alive yet

What do you think ?

Conclusions

- In times of genomics
- Big data, Genotyping is getting damn cheap
  - Whole genome sequence: ~ € 700
  - 50,000 SNP markers: ~ € 20
- Improved understanding of genetic mechanisms
- Mendelian traits offer a good entry !
  - Big effects are easier to investigate
  - We know better what we are looking for

Thank you very much!

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