Whole genome sequencing of livestock: insight in the genetics and molecular mechanisms underlying selection

Martien Groenen

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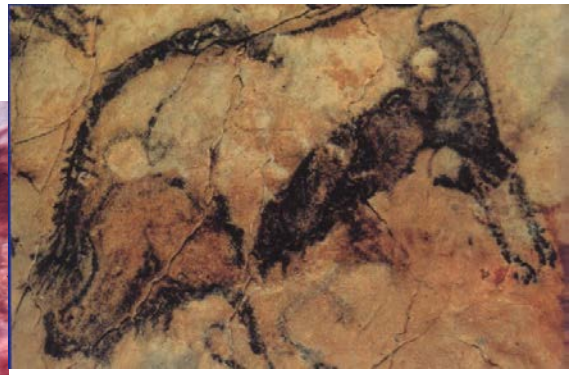
Domestication and breeding of livestock: 10,000 years of selection

- What changes have occurred in the genomes of these animals and what can we learn from it?



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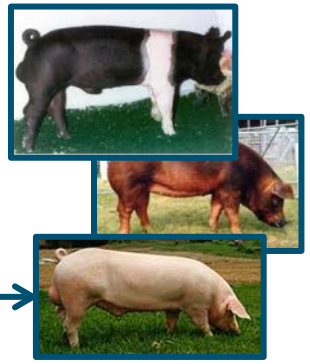
Today's talk: 1 million years of genetic change and selection in the pig (*Sus scrofa*)

European–Asian split ~ 1 Mya

Wild boar Europe

Strong selection within specific breeding lines since 1950's

European domestic



Stronger bottleneck during last ice age in European wild boar

1 Mya — 20 Kya — 10 Kya — 200 ya

Wild boar Asia

Independent domestication of Sus scrofa in Europe and Asia

Introgression of Asian haplotypes into European domestic breeds in the 18th and 19th century

Asian domestic

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Split between European and Asian wild boar: Tree based on 1 million random SNPs

African Suids

10 Mya

1 Mya

2 Mya

0.5 Mya

4 Mya

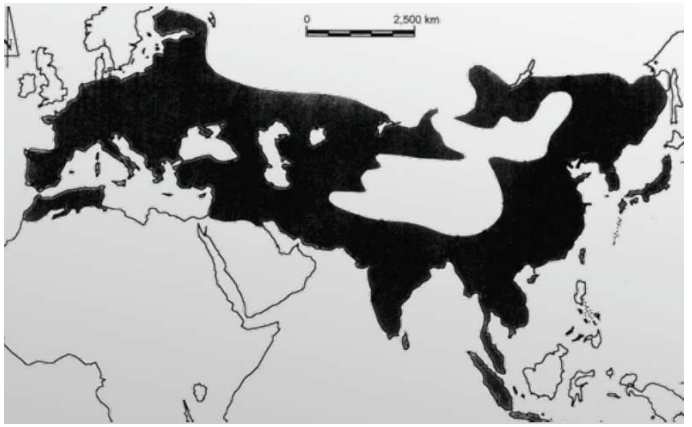
European WB

North Asian WB

South Asian WB

Sus scrofa Sumatra

Other species of the genus Sus (Indonesia, Philippines)



Frantz et al (2013) Genome Biology

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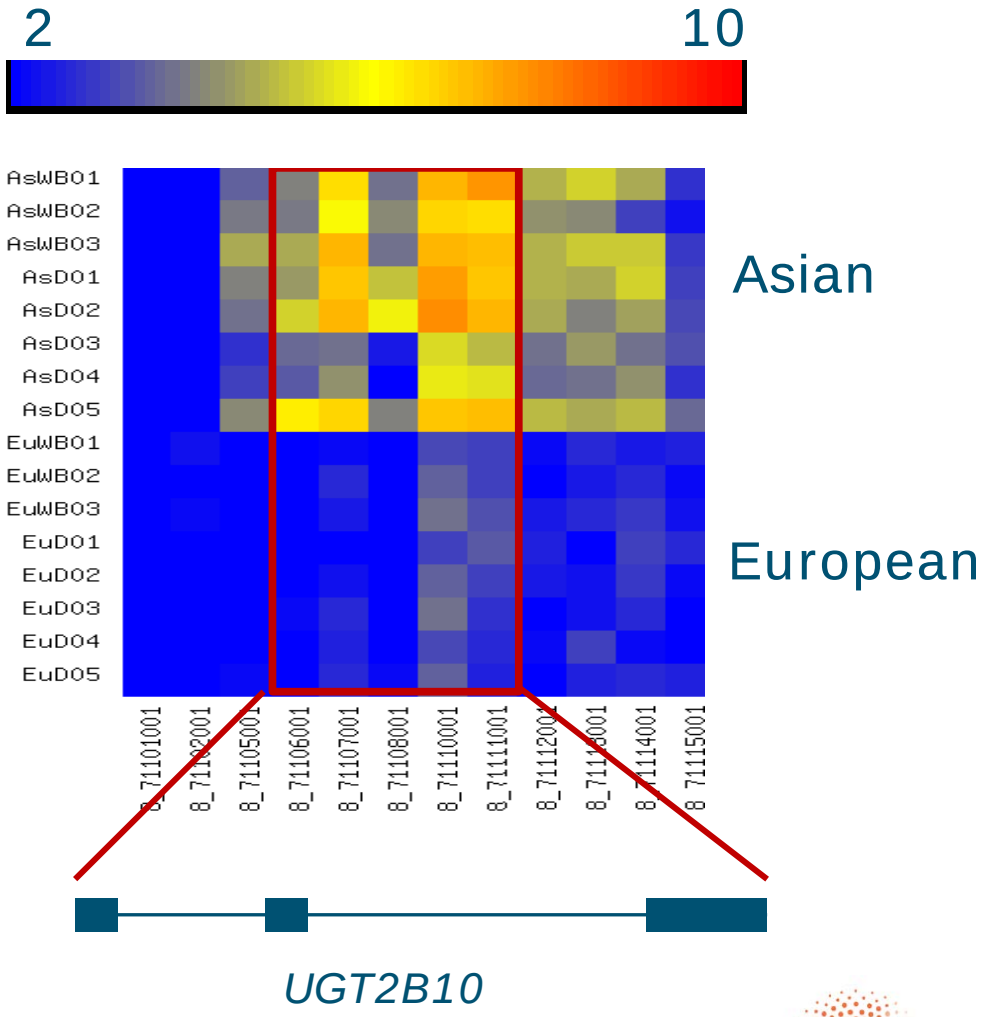
Differentiation of European and Asian wild boar

- More than 1.2 million fixed differences between the genomes of these pigs
- 5% of the genes (1191) code for different protein variants
- genes involved in sensory perception, immunity and host defense are among the most rapidly evolving genes
- Lower nucleotide diversity in European wild boar
- Fixed differences in copy number of specific genes

Groenen et al (2012) Nature 491:393-398

Fixed differences in copy number of specific genes

- Fixed duplication of the *UGT2B10* gene in Asian wild boar
- UDP glucuronosyltransferase is a hepatic enzyme involved in detoxification
- Differences in diet



Paudel et al (2013) BMC genomics

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Inference of demographic history of wild boars

Changes in effective population size between Eu-Asia divergence and domestication of WB in Europe and Asia

Wild boar Europe

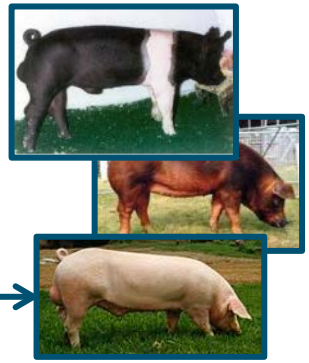
1 Mya

20 Kya

10 Kya

200 ya

European domestic



Wild boar Asia

Asian domestic

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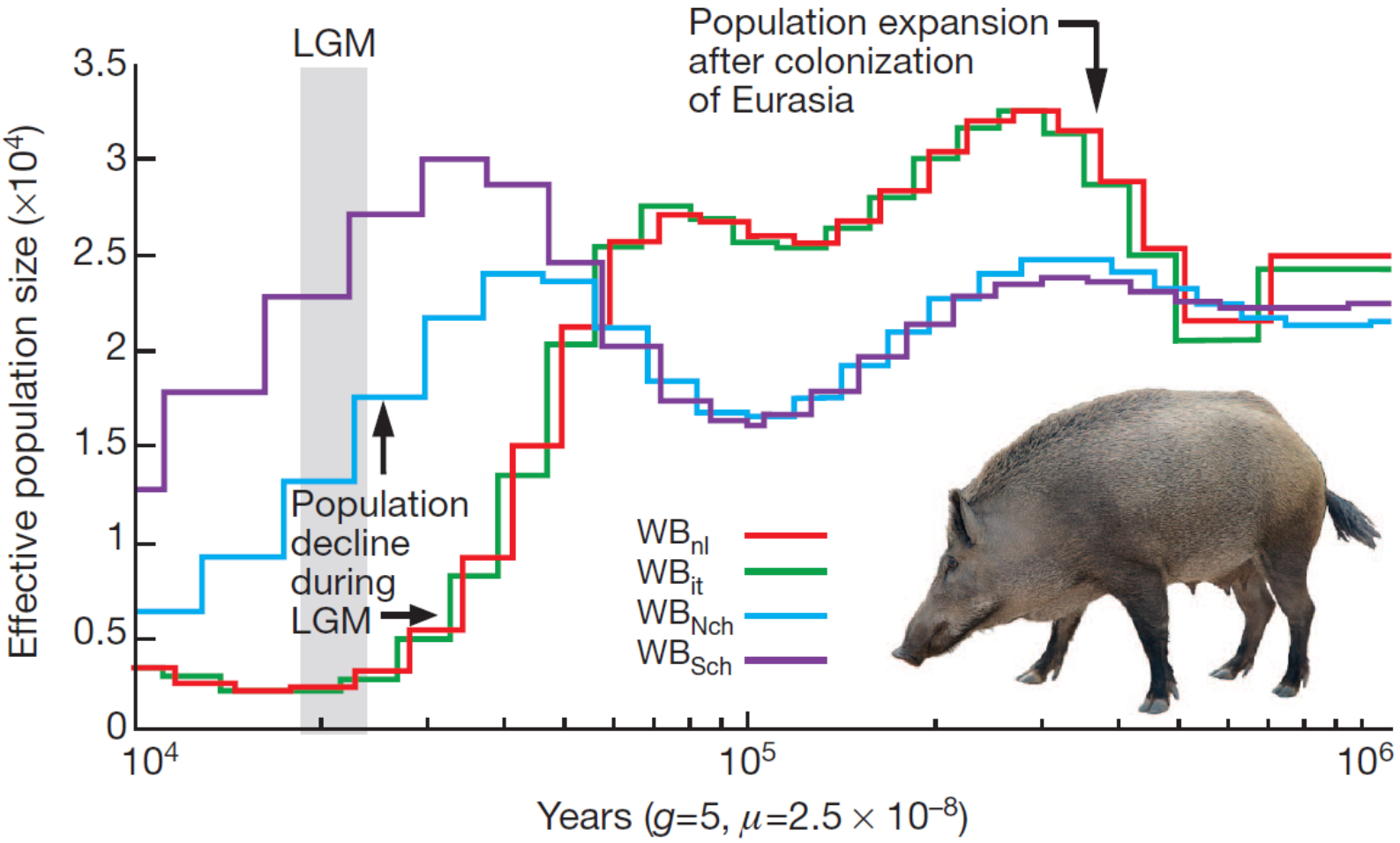
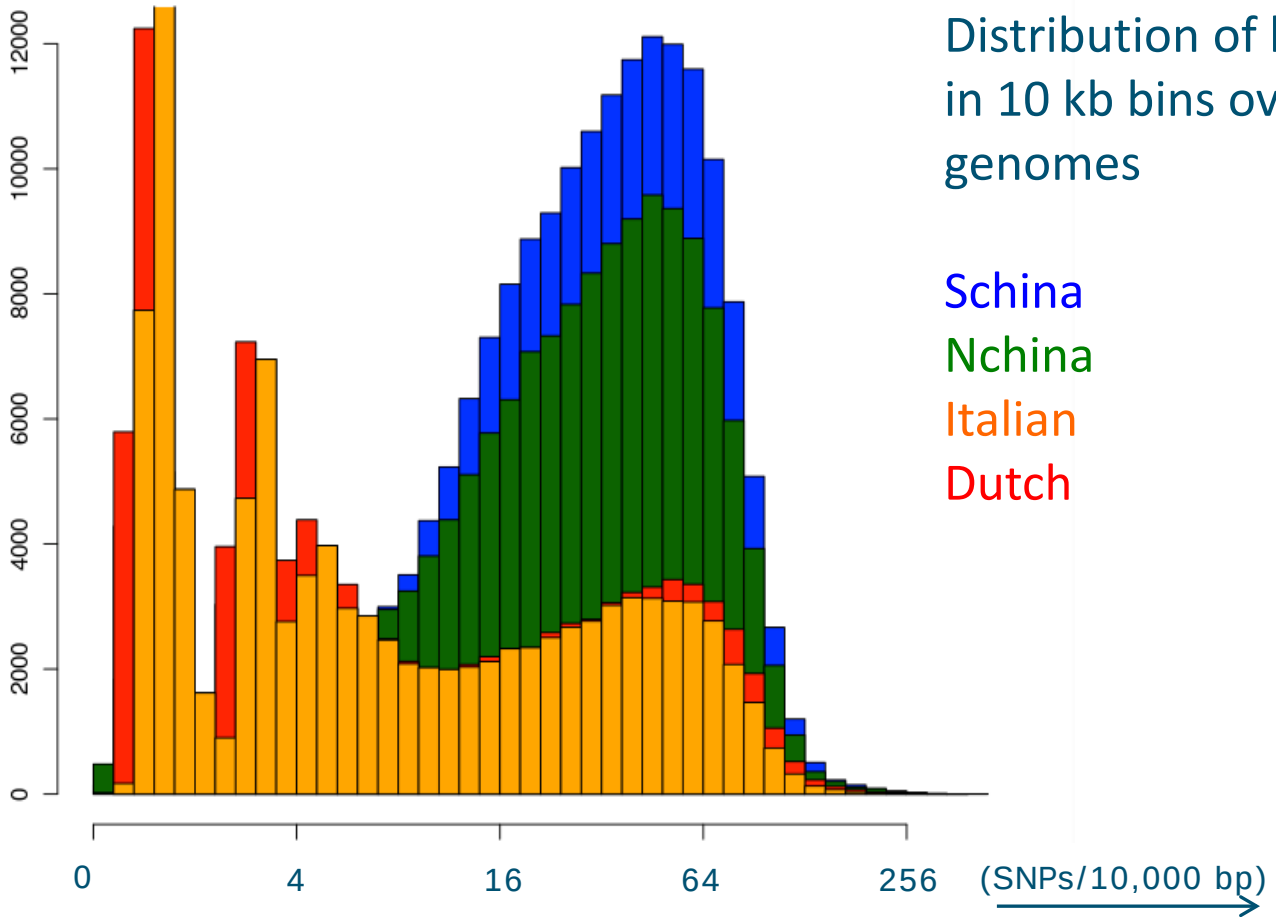
Stronger bottleneck in European wild boar during last ice age



Groenen et al (2012) Nature 491:393-398

Stronger bottleneck in European wild boar: Higher SNP variation in Asian populations



Distribution of heterozygosity in 10 kb bins over individual genomes

Schina
Nchina
Italian
Dutch

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Groenen et al (2012) Nature 491:393-398

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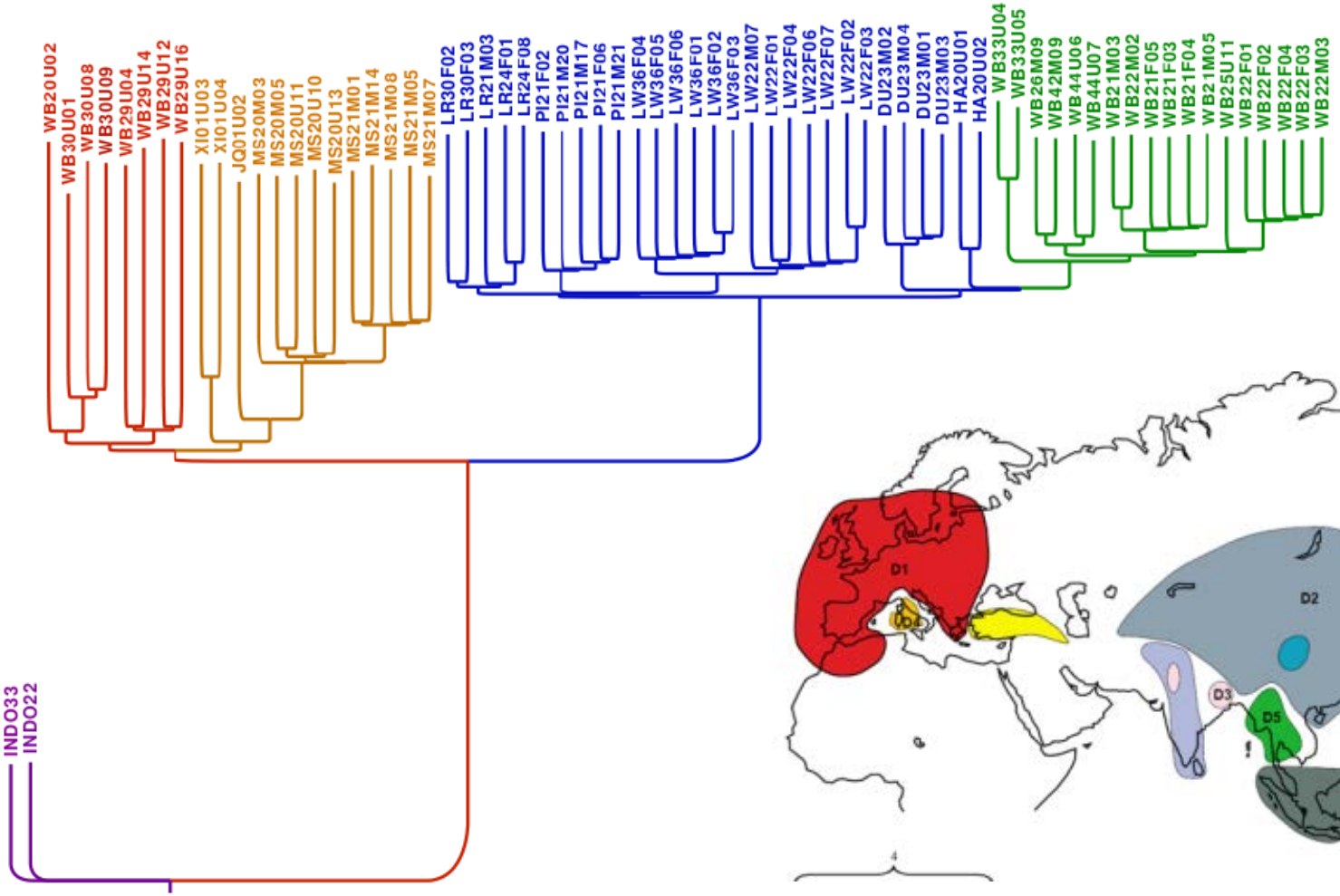
Independant domestication in Asia and Europe

Asia wild boar Asian domestic European domestic European wild boar



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Distinct differences during the domestication process in Asia and Europe

Europe:

- Until the late middle ages use of pannage where pigs were freely roaming the forest and fed on mast
- Selection on similar features as wild boar
- interbreeding with wild boar
- For a long time domestic pigs still showed many characteristics of wild boar

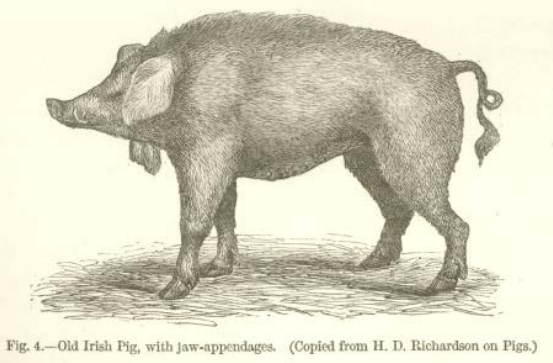

Fig. 4.—Old Irish Pig, with jaw-appendages. (Copied from H. D. Richardson on Pigs.)

Illustration from Charles Darwin's book "The Variation of Animals and Plants under Domestication " (1868)

Illustration from 15th-century French manuscript Les Très Riches Heures du duc de Berry

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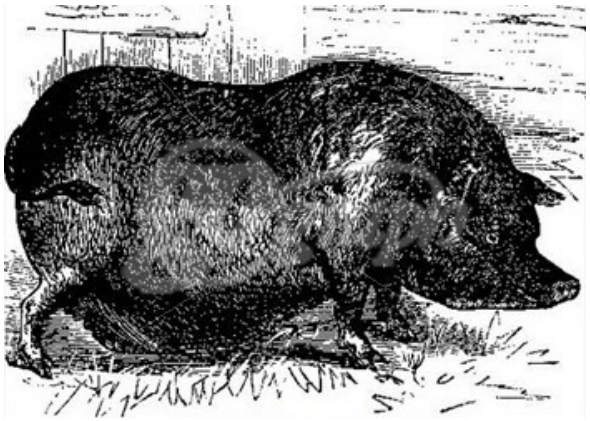
Distinct differences during the domestication process in Asia and Europe

Asia:

- Housed in enclosures
- Fed on human scraps and refuge
- Selection on rapid growth and prolific breeding
- Round, pot-bellied, small, short legs, highly prolific



From the Memorial Edition of Thomas Bewick's Works, vol III: A general History of Quadrupeds (Newcastle-upon-Tyne: Bernard Quatich, 1885)

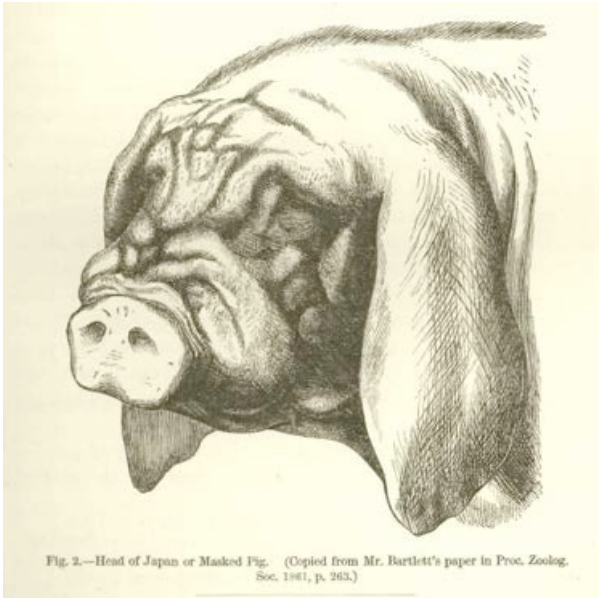


Fig. 2.—Head of Japan or Masked Pig. (Copied from Mr. Bartlett's paper in Proc. Zoolog. Soc. 1861, p. 263.)

Illustration from Charles Darwin's book "The Variation of Animals and Plants under Domestication " (1868)

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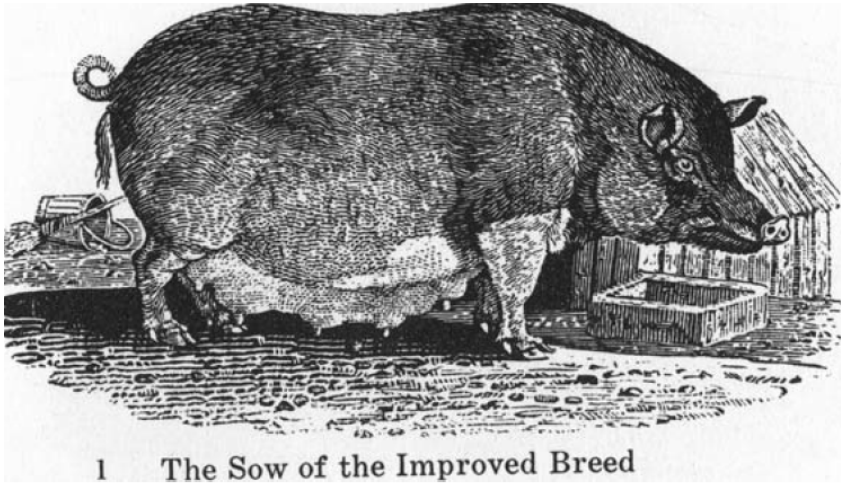
Improved pig breeds by introgression of Asian breeds in the 18th and 19th century



From the Memorial Edition of Thomas Bewick's Works, vol III: A general History of Quadrupeds (Newcastle-upon-Tyne: Bernard Quatich, 1885)

Gloucester Old Spot. Painting by John Miles 1834

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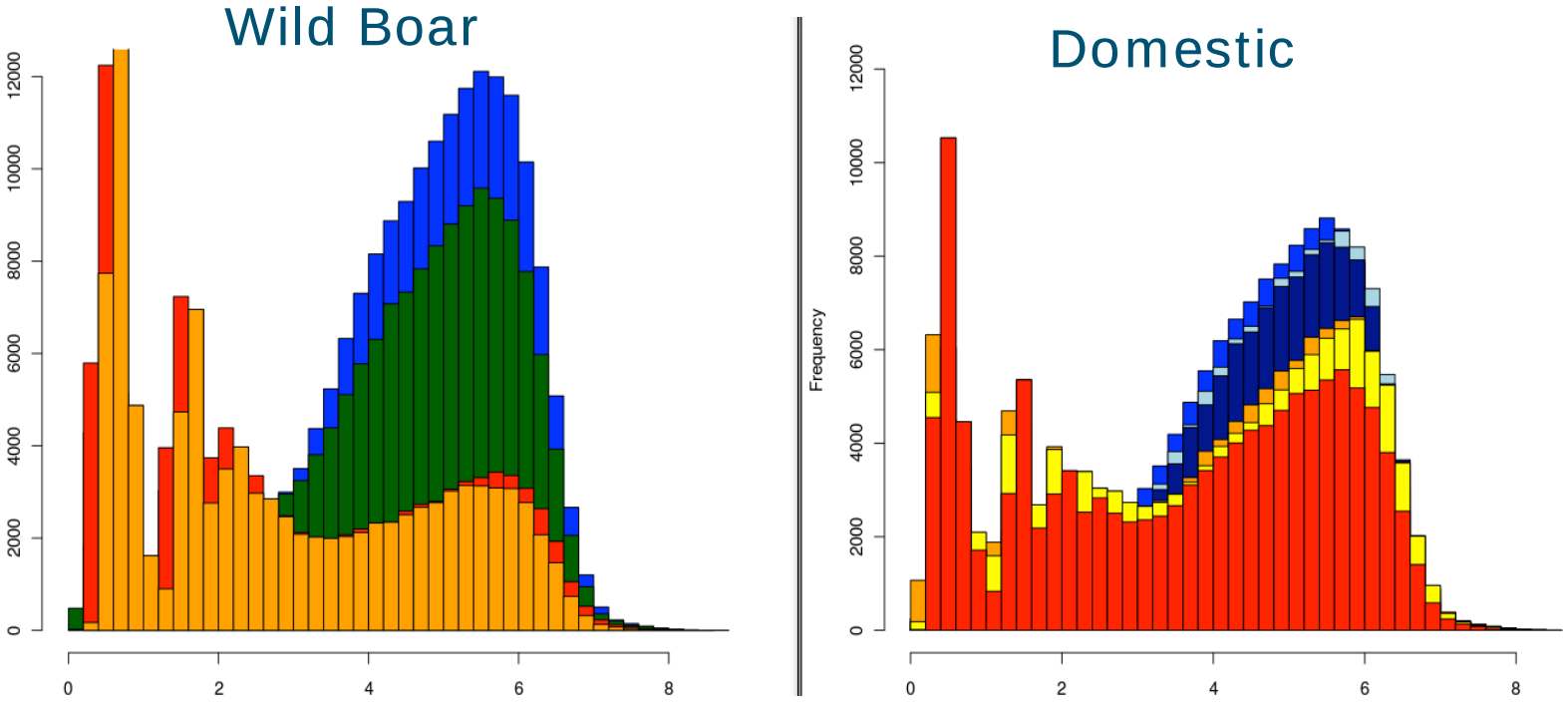
Increased SNP variation in European breeds as a result of Asian introgression



Distribution of heterozygosity (log2(SNPs) per 10kbin) over individual genomes

A: Wild Boar:SChina, NChina, Italian, Dutch

B: Breeds: blue=Chinese breeds, red-yellow=European breeds

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Groenen et al (2012) Nature 491:393-398

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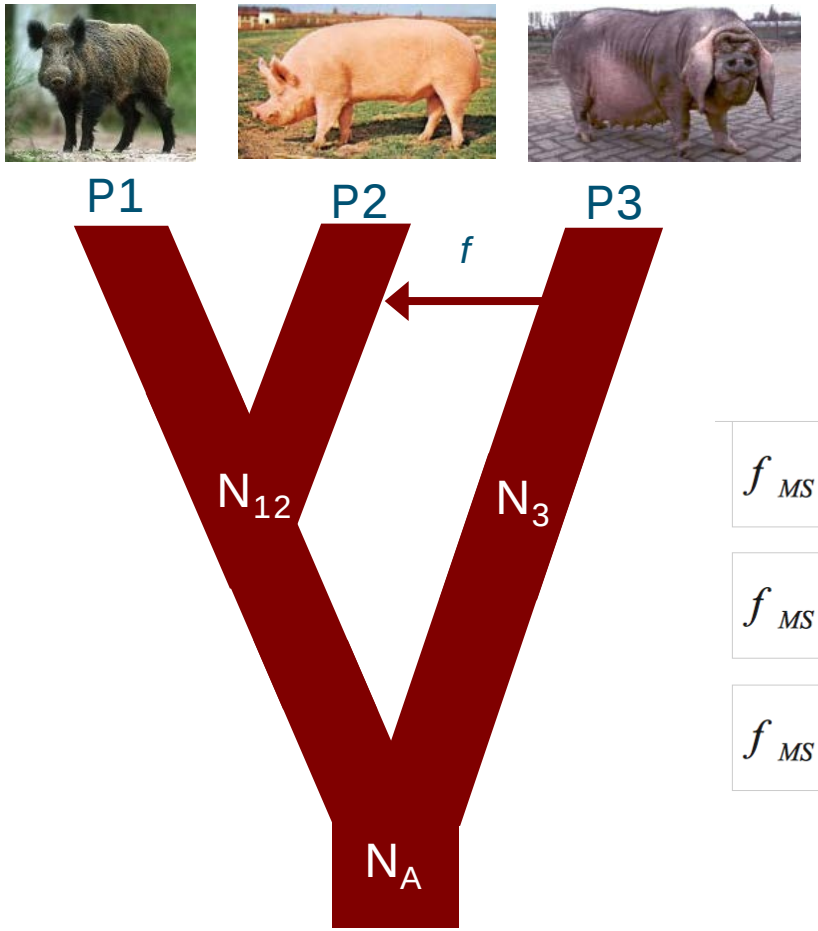
D-statistics suggest introgression of ~ 35% Asian sequence into European breeds



$$f_{MS,HA} = \frac{S(WBNL, HA, MS)}{S(WBNL, JQ, MS)} = 0.33$$

$$f_{MS,LR} = \frac{S(WBNL, LR, MS)}{S(WBNL, JQ, MS)} = 0.38$$

$$f_{MS,LW} = \frac{S(WBNL, LW, MS)}{S(WBNL, JQ, MS)} = 0.38$$

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- Results presented so far show how WGS data provides insight in European and Asian *Sus scrofa* evolution, population demography and admixture

- What does WGS data tell us about selection for specific genes related to specific traits during domestication and more recent pig breeding?

Signatures of selection and introgression in the genome of domestic pigs

- Medium-high density SNP genotyping in combination with genome sequencing

  Wilkinson et al. (2013) PLoS genetics

- Sequencing pools of different breeds

  Rubin et al. (2012) PNAS

- Whole genome sequencing of individual pigs

  Bosse et al (2013) in preparation

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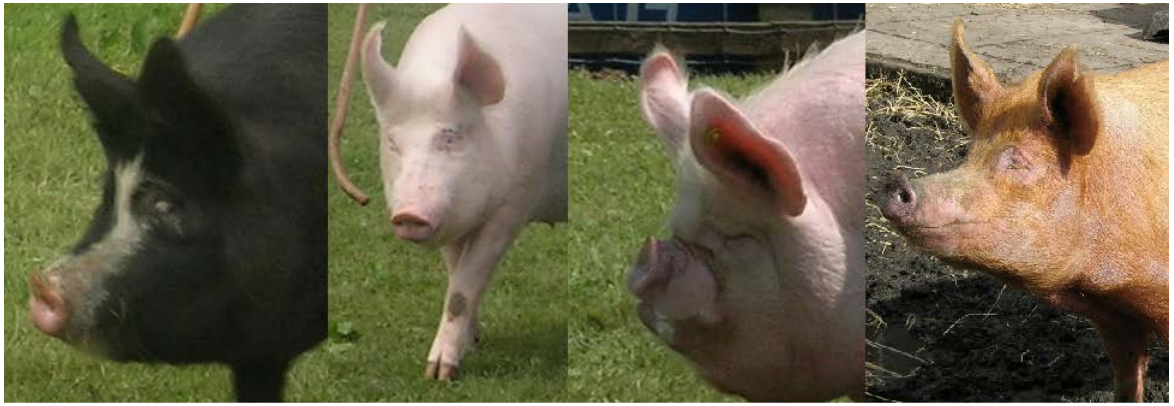
Differences in coat colour, facial and ear morfologie:



Berkshire | Large White | Middle White | Tamworth

Prick eared breeds

Flat eared breeds

British Saddleback | Gloucestershire Old spots | Large Black

Wilkinson et al. (2013) PLoS genetics

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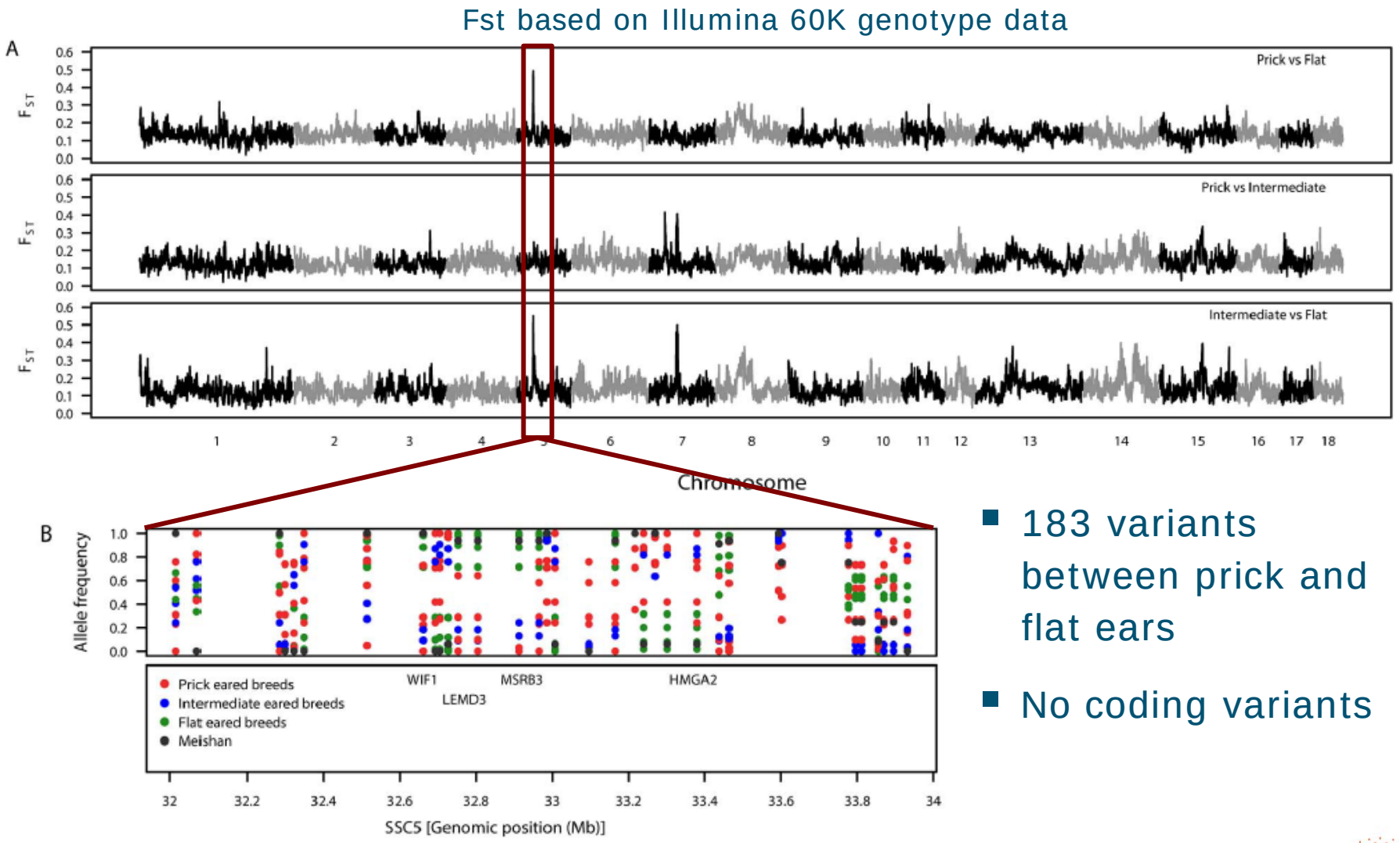
Genetic variation associated with ear phenotypes



- 183 variants between prick and flat ears
- No coding variants

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  Bosse et al (2012) PLoS genetics 9:

  Bosse et al (2013) submitted

For centuries man has selected coat colour in pigs

Detail of the fresco *Effetti del Buongoverno in Campagna* in the Palazzo Pubblico in Siena, Italy painted by Ambrogio Lorenzetti in 1337 showing a white belted pig

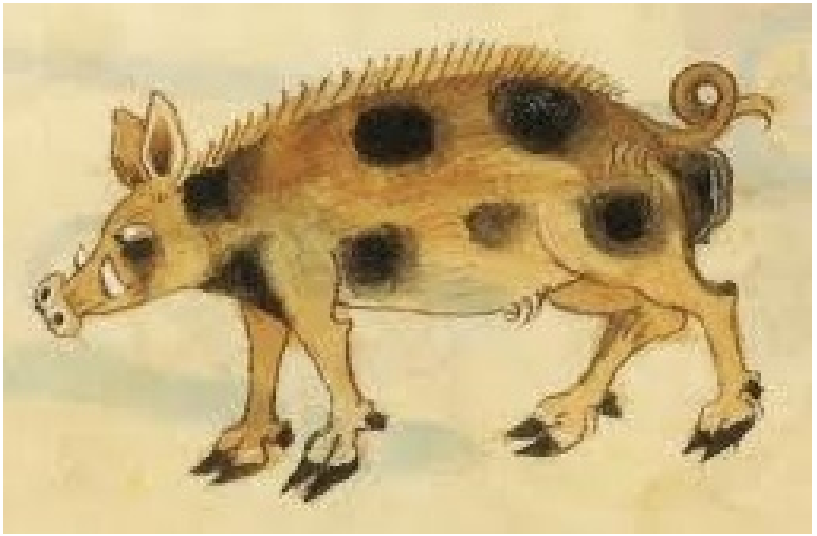
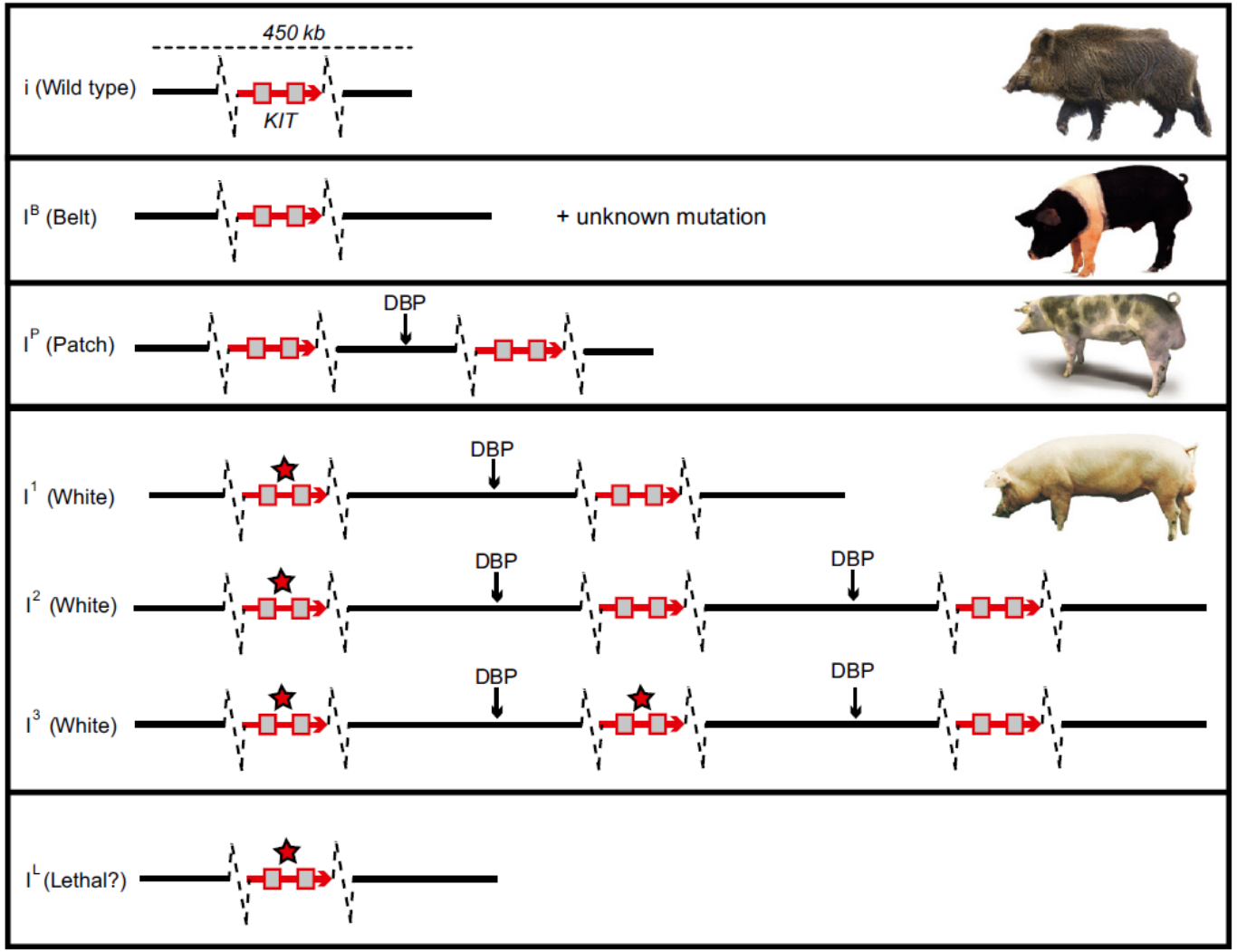


image of a spotted pig from the fourteenth-century *Luttrell Psalter*

Duplication of KIT gene affects coat colour



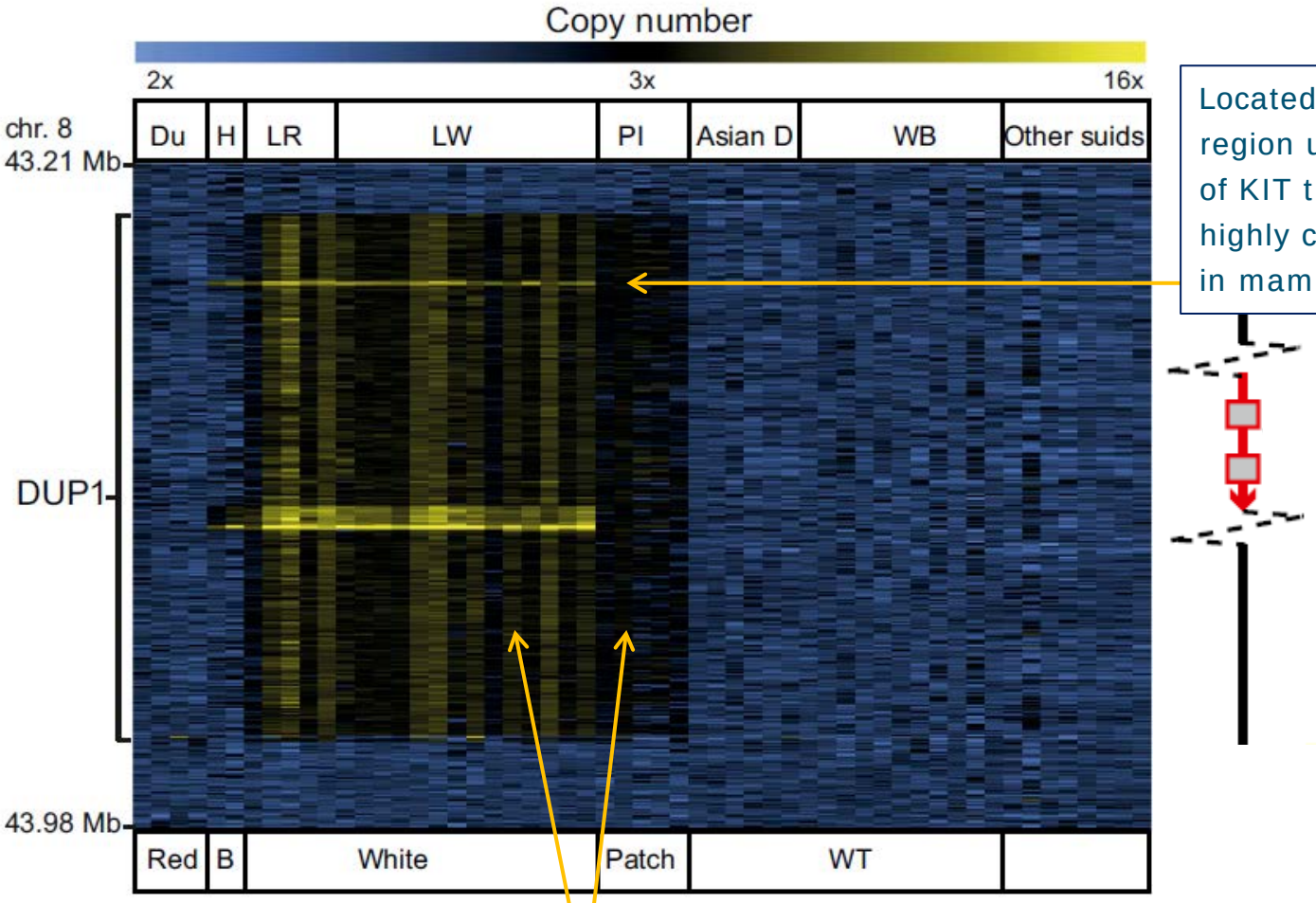
Rubin et al. (2012) PNAS

Identification of belted allele using a NGS read depth CNV analysis

Hampshire(H)

Large White (LW)

Pietrain(PI)



Located in a region upstream of KIT that is highly conserved in mammals

Different haplotypes in white and patch suggests independent duplication event of the same segment

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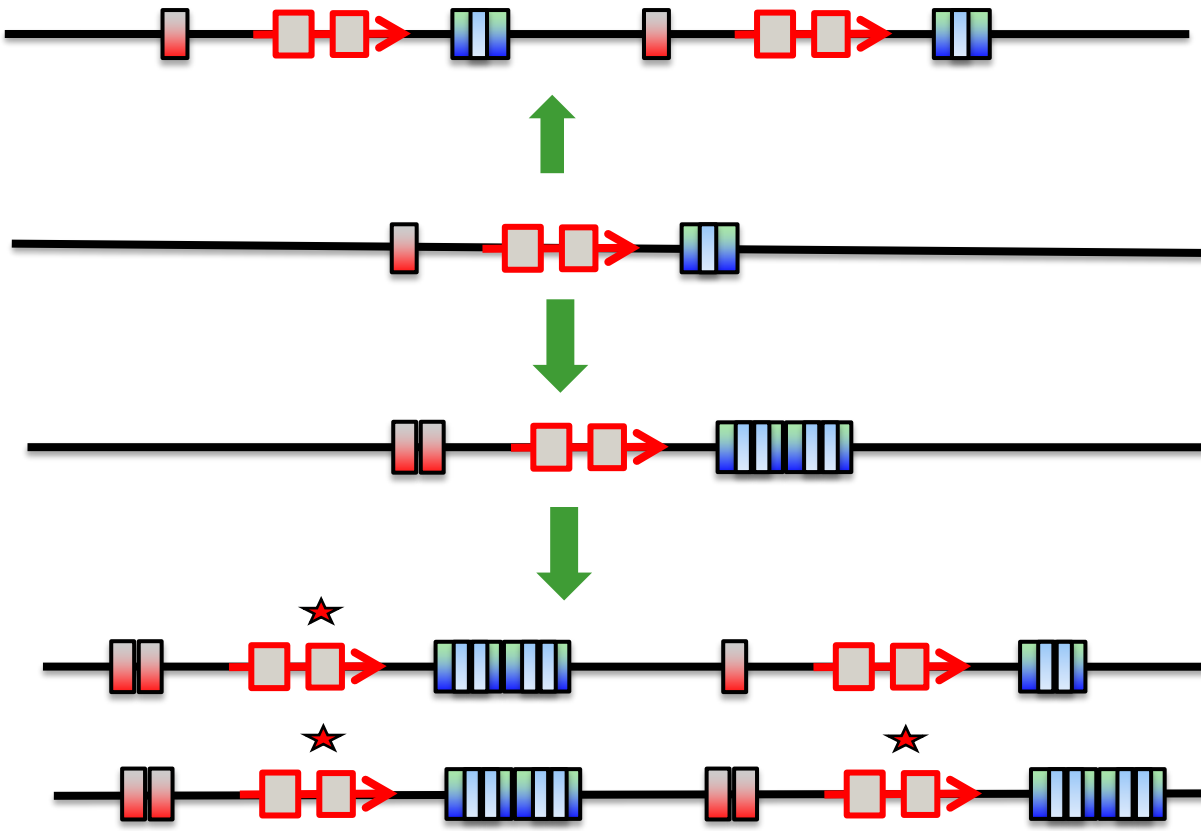
KIT alleles: Complex organization resulting from multiple independent duplications



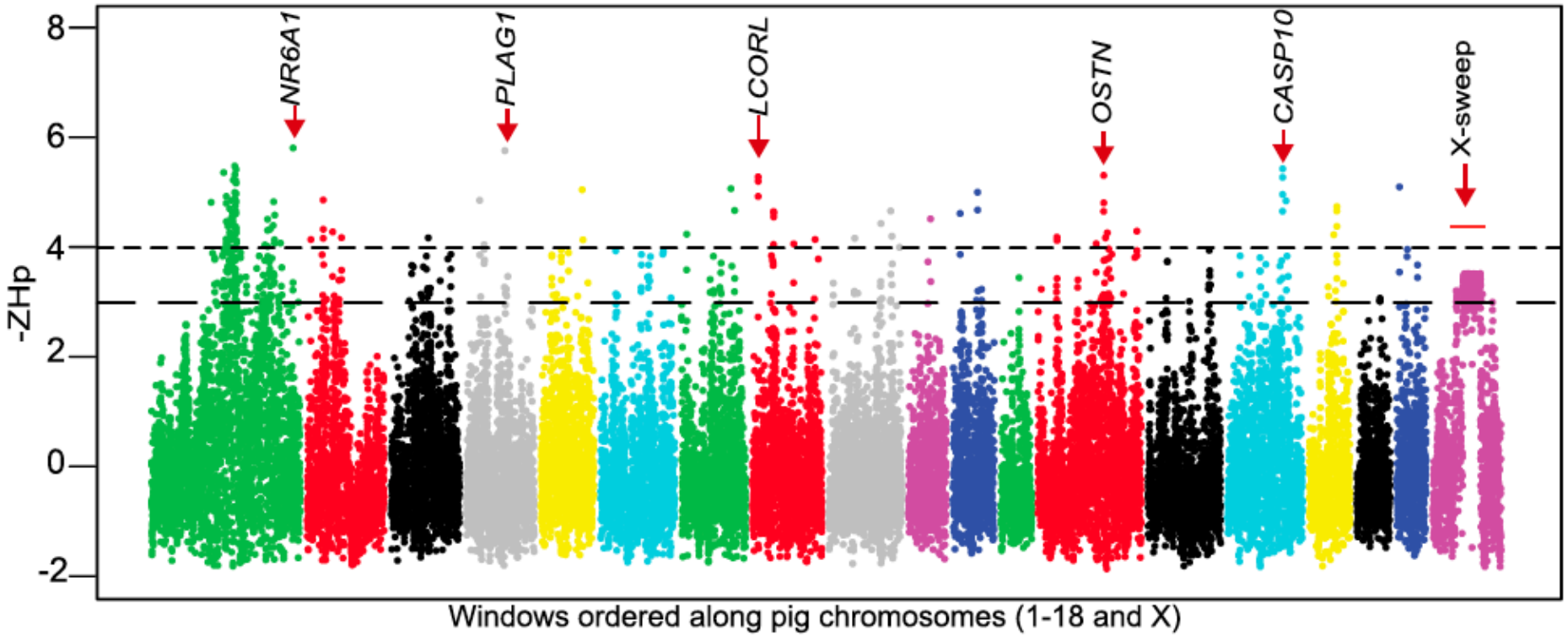
Patch

Wild type

Belt

Dominant white

Selective sweeps in European domestic pigs

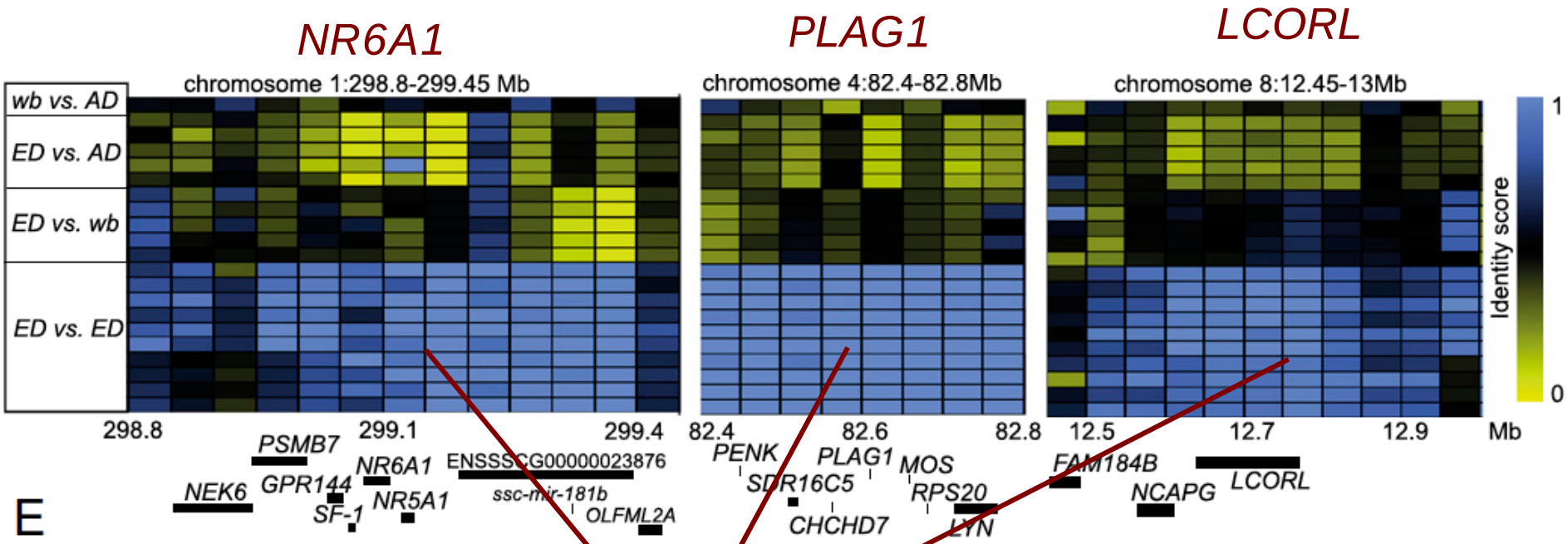


QTL for number of vertebrae

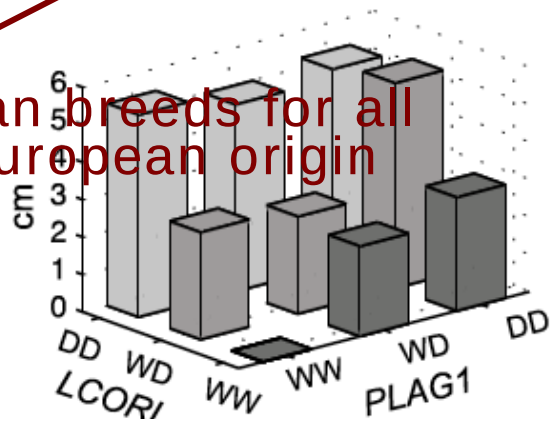
QTL for body length

Rubin et al. (2012) PNAS

Haplotype sharing in European domestic pigs



Haplotypes in European breeds for all three regions are of European origin



Rubin et al. (2012) PNAS

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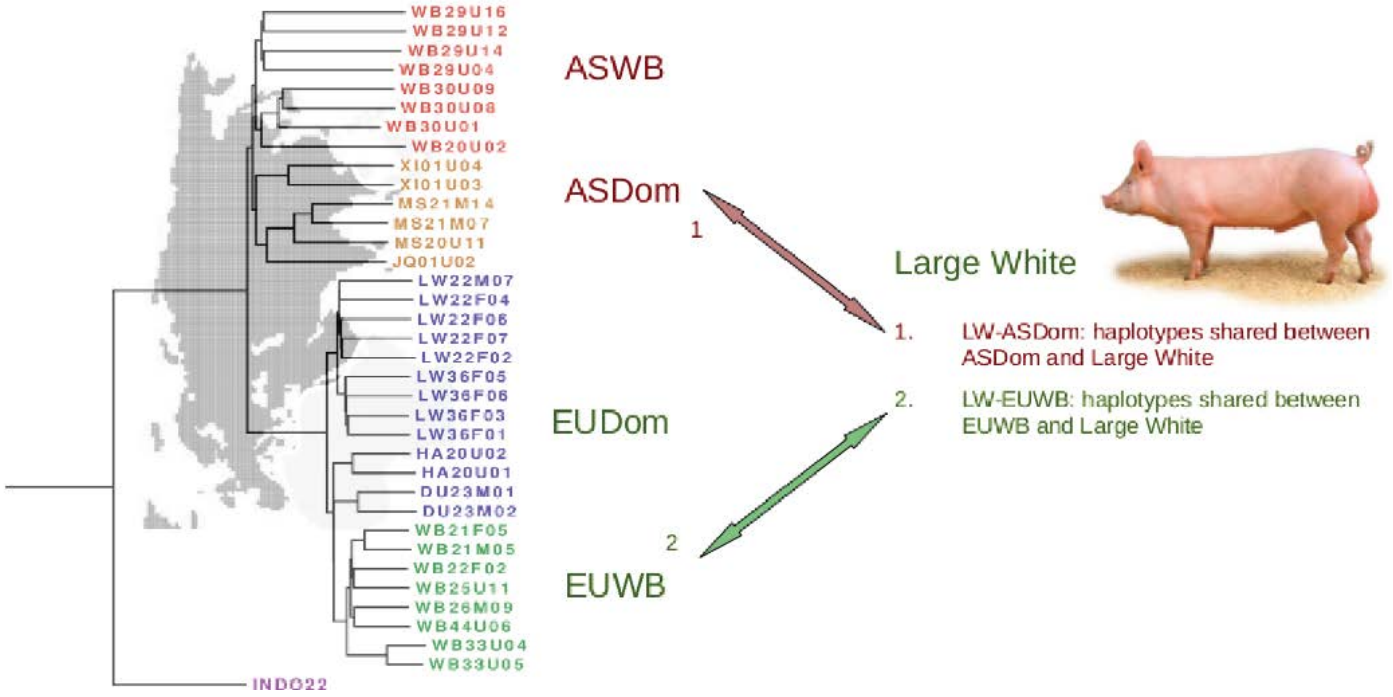
European vs Asian origin of haplotypes across the genome

- SNPs identified from individually sequenced genomes
- Reconstruct haplotypes with Beagle



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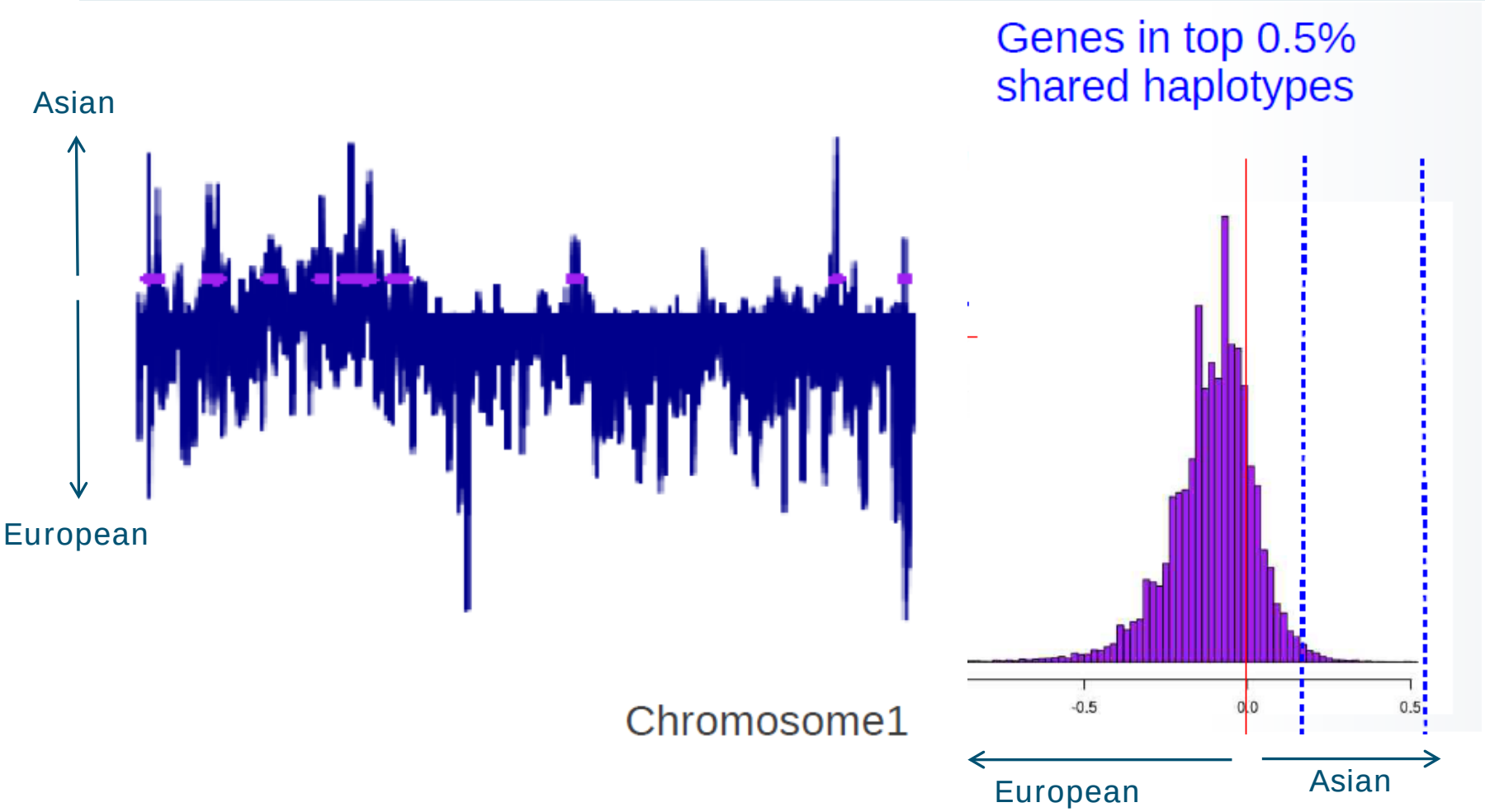
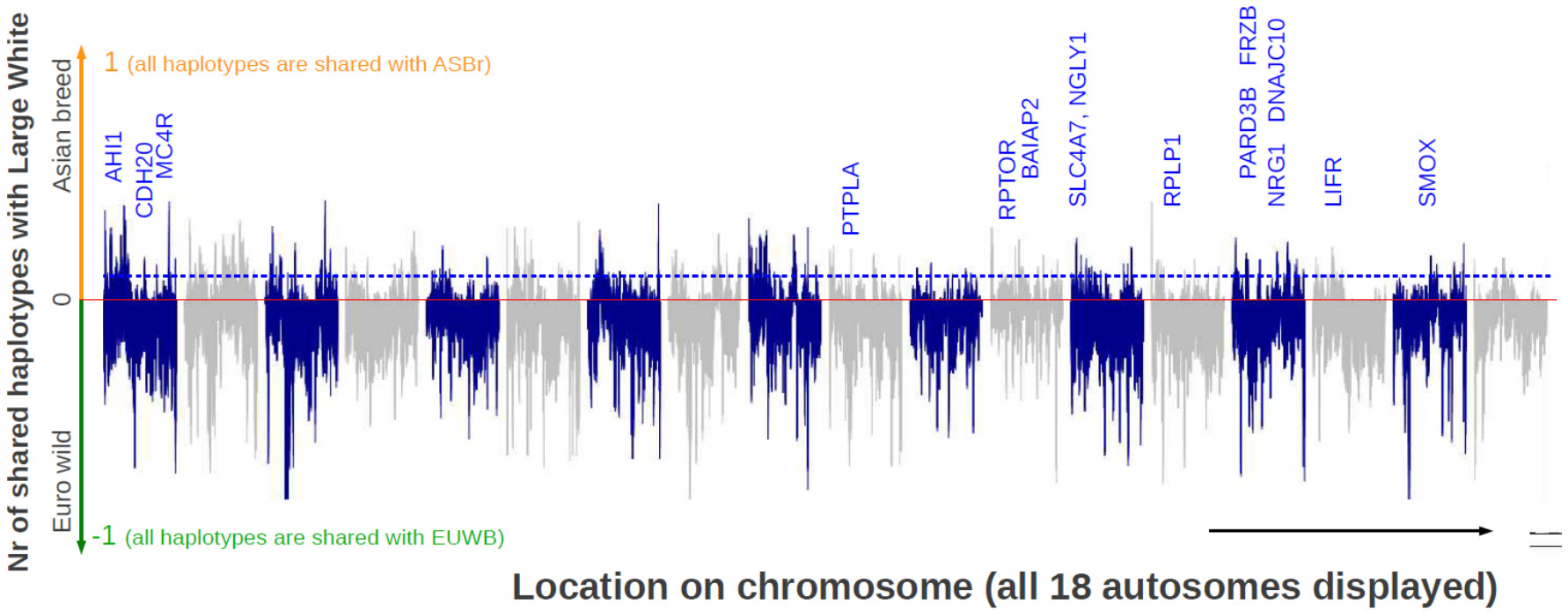
Comparison LW shared haplotypes with Asian and European wild boar



Bosse et al. (2013) submitted

Genes in top 0.5% shared Asian haplotypes



- Identified non-synonymous mutations under selection
- Tested in GWAS study (fertility)
- Results show selection on fertility after introgression of Asian haplotypes

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Bosse et al. (2013) submitted

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Take home messages

- WGS data of a few individuals provides detailed insight into evolution, population history and demography
- WGS data of defined populations provides powerful data for the identification of selective sweeps
- Variation in phenotypes result from single nucleotide variation as well as from complex genome rearrangements
- Well defined phenotypes are essential

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