Genes and Hereditary in Dogs: from breed specific characteristics to inherited diseases

Kirsi Sainio

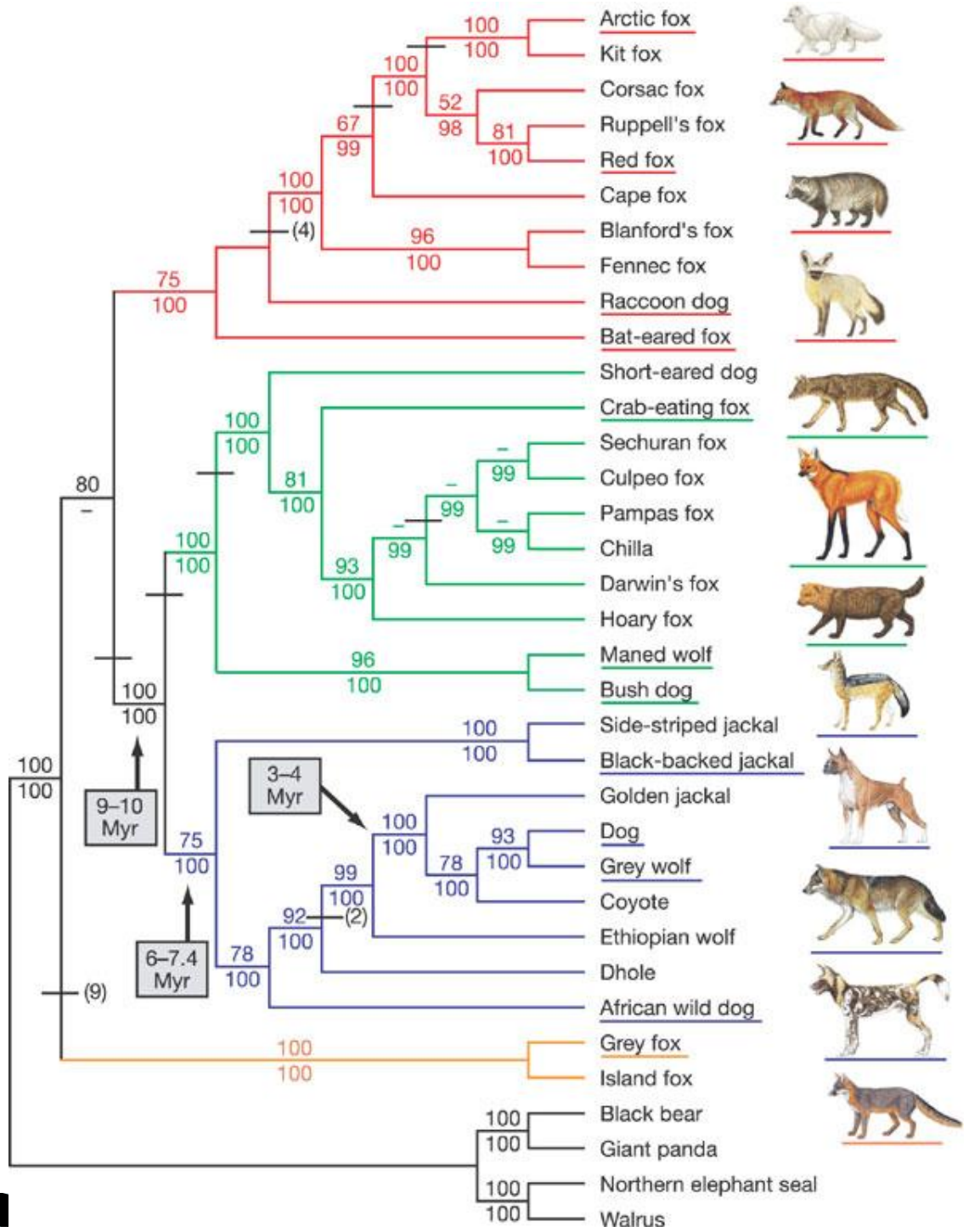
Some facts about dogs

Dog

- *Canis lupus familiaris* domesticated from wild Grey Wolf in South-Eastern Asia some 30.000-15.000 years ago – earliest fossiles 30.000 years old
- There is no generally accepted picture of where, when, and how the domestic dog originated

Phylogenetic tree of the dogs

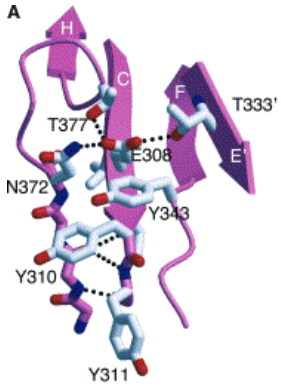
- Red fox strain (red), South American strain (green), “Wolf” strain (blue), “grey- and Island Fox” strain (orange)
- Strain separation given in million years (Myr)



What makes a dog dog – or a wolf?

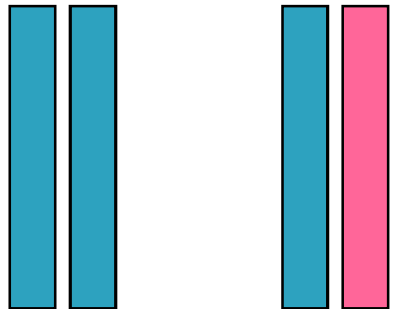
- Number of chromosomes is species specific
- Dog and wolf has 39 pairs (2n = 78) of chromosomes
- Every cell in the body has this double amount of chromosomes = genome
- Germ cells have single number of chromosomes (n= 38 + X or Y)
- In fertilization the chromosome number is again doubled

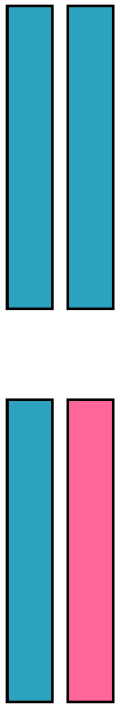
Some facts about the genes



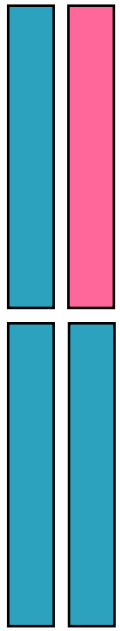
- **Gene** = basic unit of heredity in a living organism – encodes for a protein
- **Genome** = species specific genes = chromosomes
- **Gene locus** = specific site for a gene in the chromosome
- **Allele** = one gene in specific locus that encodes for one protein – gives one phenotypic character in an individual

  - alleles - as chromosomes - form pairs





- **Homozygote**= individual with two identical gene alleles, one inherited from each parent
- **Heterozygote**= individual with two non-identical alleles of a particular gene



- **Dominance** = single allele gives a phenotype
- **Recessive** = hidden gene, gives phenotype only when the individual has to identical copies of the gene
- **Polygenic** = severeal genes are affective at the same time to give a phenotype
- **Multifactorial** = polygenetic trait where also environmental factors affect the phenotype

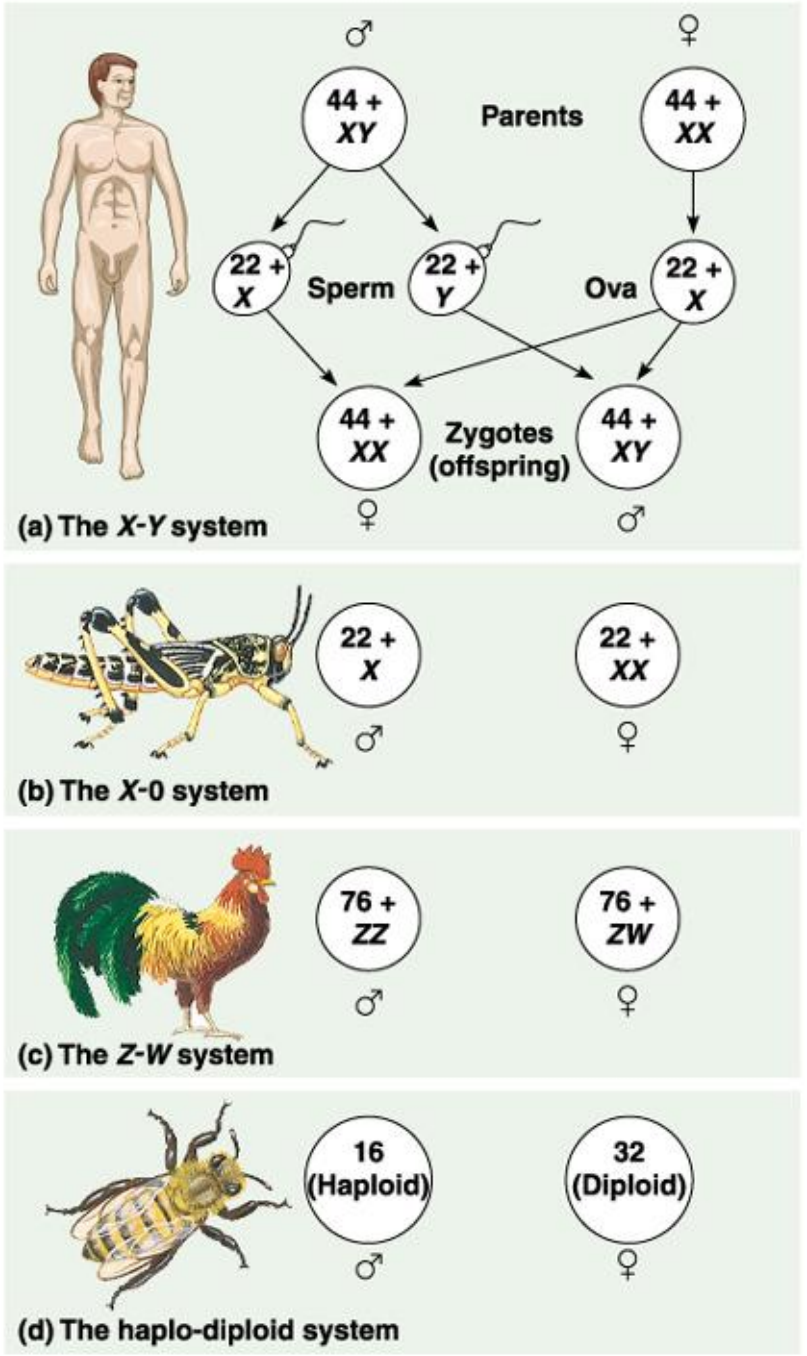
Inherited features

- Autosomal dominant
- Autosomal recessive
- X-kromosomal
- Polygenic and multifactorial

Why X-chromosomal, where is Y?

- Scientists say deciphering the genetic code of the Y chromosome is a small but important step in understanding the deep biological differences between males and females.
- At the moment in human there are more than 2000 different genes found in X-chromosome but only 78 in Y.

Sex determination in different species

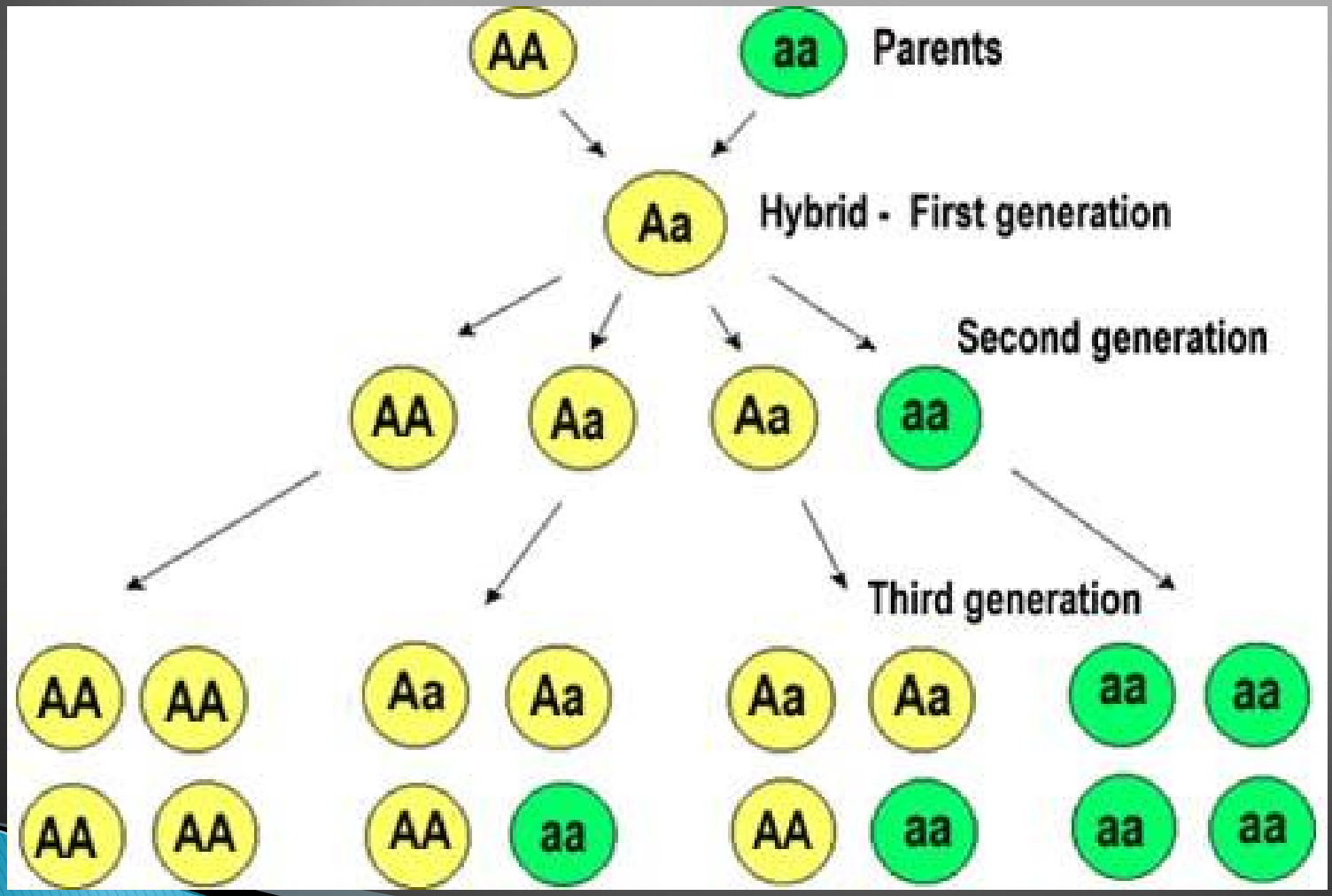


From genes to heredity

GREGOR MENDEL

Planting the Seeds of Genetics

Mendelian inheritance



Mendelian inheritance

- Mendel cultivated and tested some 29,000 pea plants
- *Mendel's Laws*:
- 1. **Law of Segregation**
  - The paternal and maternal chromosomes get separated and the alleles with the traits of a character are segregated into two different gametes. Thus a gamete will receive one allele or the other (randomly)

Mendelian inheritance

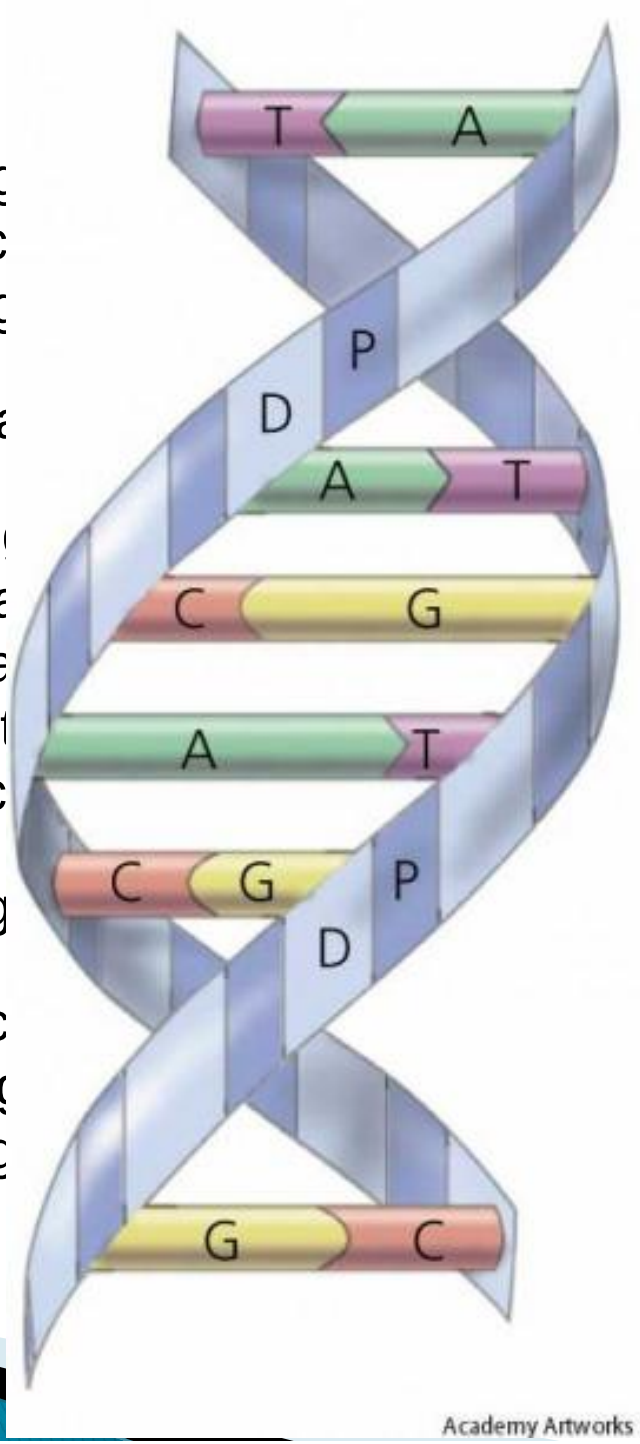
- 2. **Law of Independent Assortment:**
  - Alleles of different genes assort independently of one another during gamete formation
  - Different traits are inherited independently of each other, so that there is no relation, for example, between a dog's colour and tail length.

Actually there are genes that are LINKED but Mendel could not show this with his peas…

Genes and mutations

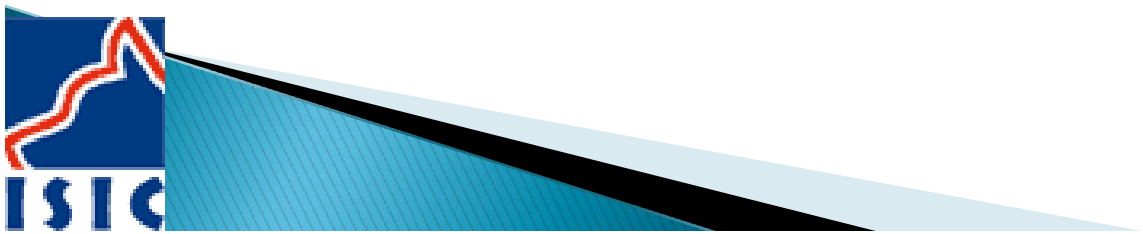
- **Structure of genes =** basic unit DNA (deoxyribonucleic acid)
- **Mutation =** change in the structure of DNA!

1 cggggccccg cgctcctg :ggatgggat tcgggccact
61 tggagttaat gtccaac cgaggtaaga gagggaaacg
121 tgctggaggg gacag ga aggcagaagg
gcgcggctgg
181 accccaagcg ggcga agg aaccggaggg
aggctagact
241 tgcggaggat aggtt g tacagacaga gaccctggtg
301 tcctggaacc ctgaaa a cctcgctctg tacagtcctg
361 gaacccagcg tgcga g cagccagcgt cttttccaga
421 gtgcaactgc agcgtt tgttgagctt gtttgggtct
481 gttctgggag aaagc :aa aggtgctgtg
aacctaaaaa .....
26341 gttcgaatgg gag gcag ggtaaagttt
gcgacggttc
26401 tttactgttg tgatc ca cttctttgga agttctgacc
26461 tctctgatgt ctcg : ctctacaaac tttatttttg
26521 tacaatatca ttttg : ttcta



Inherited phenotypes

- Most breed specific charateristics, such as colour, hair structure, overall construction - anything that makes the dog different from the Asian Grey Wolf - are caused by *mutations*!



How mutations are inherited?

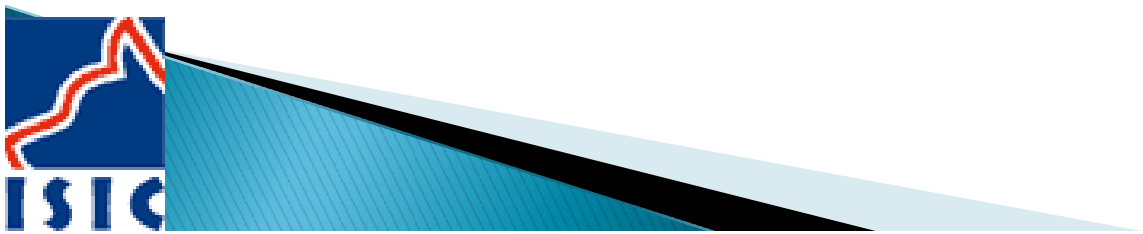
- Mutations are not rare, many somatic diseases such as cancer are caused by mutations
- Inherited characteristics – and diseases are caused by mutations in GERM LINE cell DNA sequence (A-T; C-G)
- In other words: only germ line mutations are inherited by the offspring!

Germ cells

Some facts about the dog genome

The Dog Genome Project

- The approach: sequencing the dog genome would make it possible to map genetic traits both in dog as well as in human
- The DNA for the project was collected from one (female) inbred (homogeneous) individual representing a relatively common breed (the Boxer called Tasha)




nature
QUANTUM MEMORY
Controlling single photons
THE GENETICS OF NONSENSE
B-cellular balancing act
IN PURSUIT OF PLEASURE
Dopamine's role revisited
THE DOG GENOME

NEWS & VIEWS

C. COLLINS/CORBIS

GENOMICS

The dog has its day

Hans Ellegren

Domestication and selective breeding have transformed wolves into the diversity of dogs we see today. The sequence of the genome of one breed adds to our understanding of mammalian biology and genome evolution.

The Dog Genome

- 78 (n=38 + X/Y) chromosomes
- The dog genome contains DNA covering appr. 2,5 billion basepairs (roughly the size of the human genome)

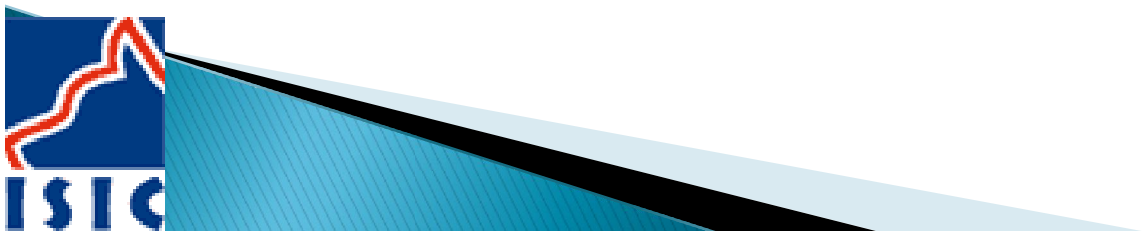
Origin of dogs and evolution of breeds

- Comparison between the Boxer sequence (covering 99% of the dog genome) and the Standard Poodle sequence (earlier sequencing project, covers 75% of the genome) with partial sequences from nine different breeds, four species of wolves and a coyote

Breed	Sequence reads
Beagle	99,648
Labrador Retriever	99,744
German Shepherd	100,743
Italian Greyhound	98,208
English Shepherd	99,648
Bedlington Terrier	102,240
Portugese Water Dog	97,728
Alaskan Malamute	100,704
Rottweiler	102,143
Chinese Gray Wolf	23,423
Spanish Gray Wolf	22,176
Californian Coyote	23,790
Alaskan Gray Wolf	21,696
Indian Gray Wolf	22,560

The Origin

- Domestication from wild wolves
- Idea: dog originates from few wild ancestors (follow of the mitochondrial DNA of females)
- Peter Savolainen et al. 2010:
  - evidence that the dog has a single origin in time and space and
  - the domestic dog originated in southern China less than 16,300 ya, from several hundred wolves, mtDNA shows six original clades



The origin and diversity

- First genetic bottleneck at the time of domestication (some 9,000 generations ago) and following bottlenecks some 30-90 generations ago (formation of the breeds)

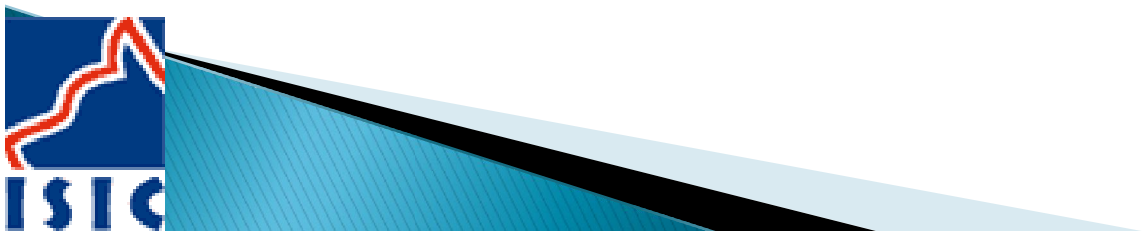



Further development of the breeds

- Breeding within smaller subpopulations
- Segregation of breeds has further *decreased the genetic diversity* at the population level
- Selective breeding has further decreased the diversity
- Other population level bottlenecks - II World War

Dog vs. human genes

- Comparison between genes
- Dog has app. 19,300 genes compared to 20,000 in humans
- Nearly all dog genes are homologous to human genes



Dog as model of human disease

- Most dog breeds have genetic traits causing disease – as humans
- Typical disease are those affecting the eyes, bone development and structure, immunological disease, rare genetic traits, autoimmune disease, metabolic disorders

Breed specific mutations = breed characteristics!

Hairless mutation

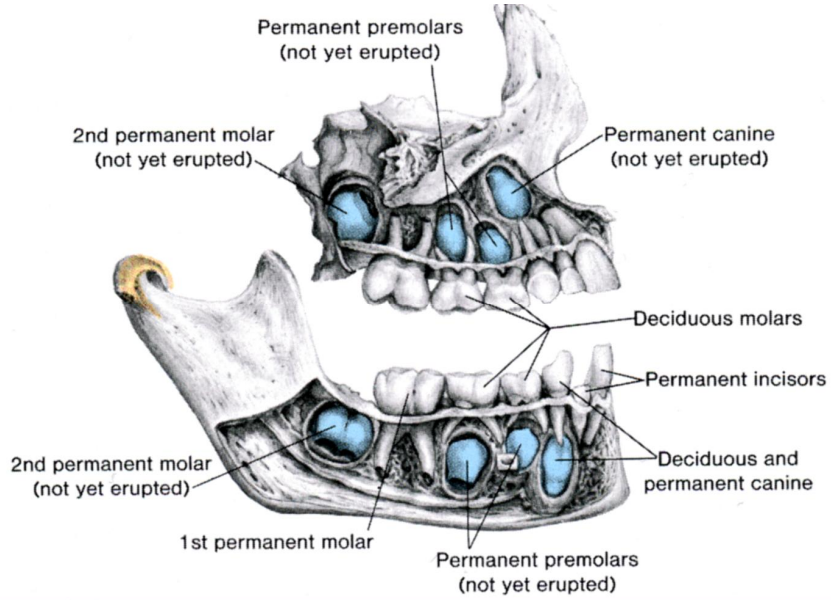
Peruvian Hairless

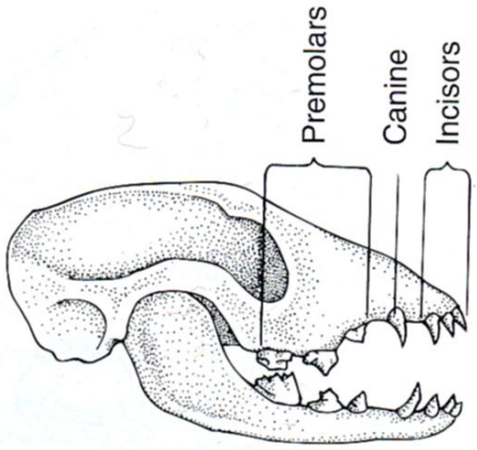
- As ancient as the human civilization history
- Ancestors of this breed were held and worshiped by Inca- and Aztec Indians
- This is not a ”bred” phenotype, but a spontaneous autosomal dominant mutation

Hairless mutation

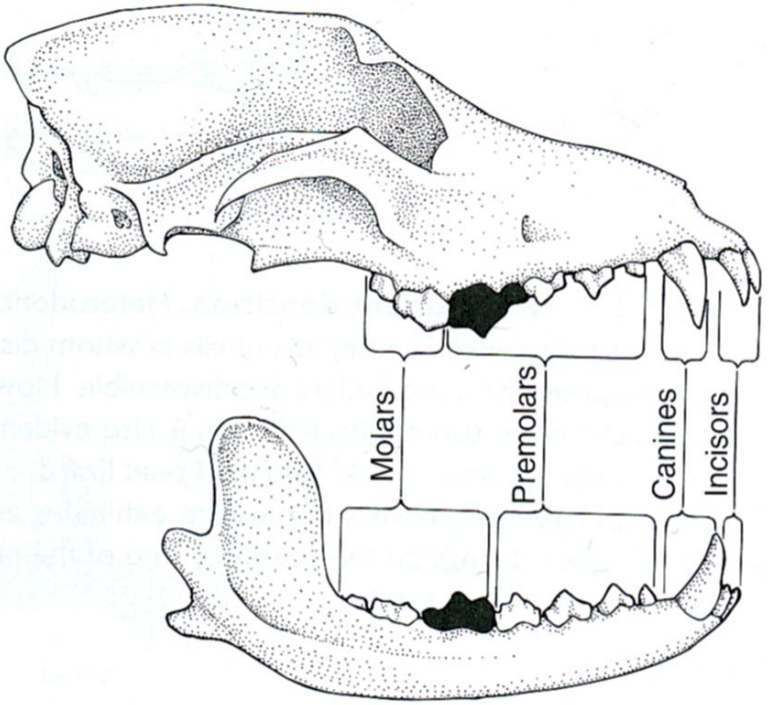
- Same mutation found in Chinese Crested and Mexican Hairless (Xoloitzcuintli)
- Autosomal dominant mutation in dog chromosome 17 at the site of Foxi3 gene (genetic deletion)
- *Foxi3* fuctions during the development of all ectodermal organs

Dog and human dentition



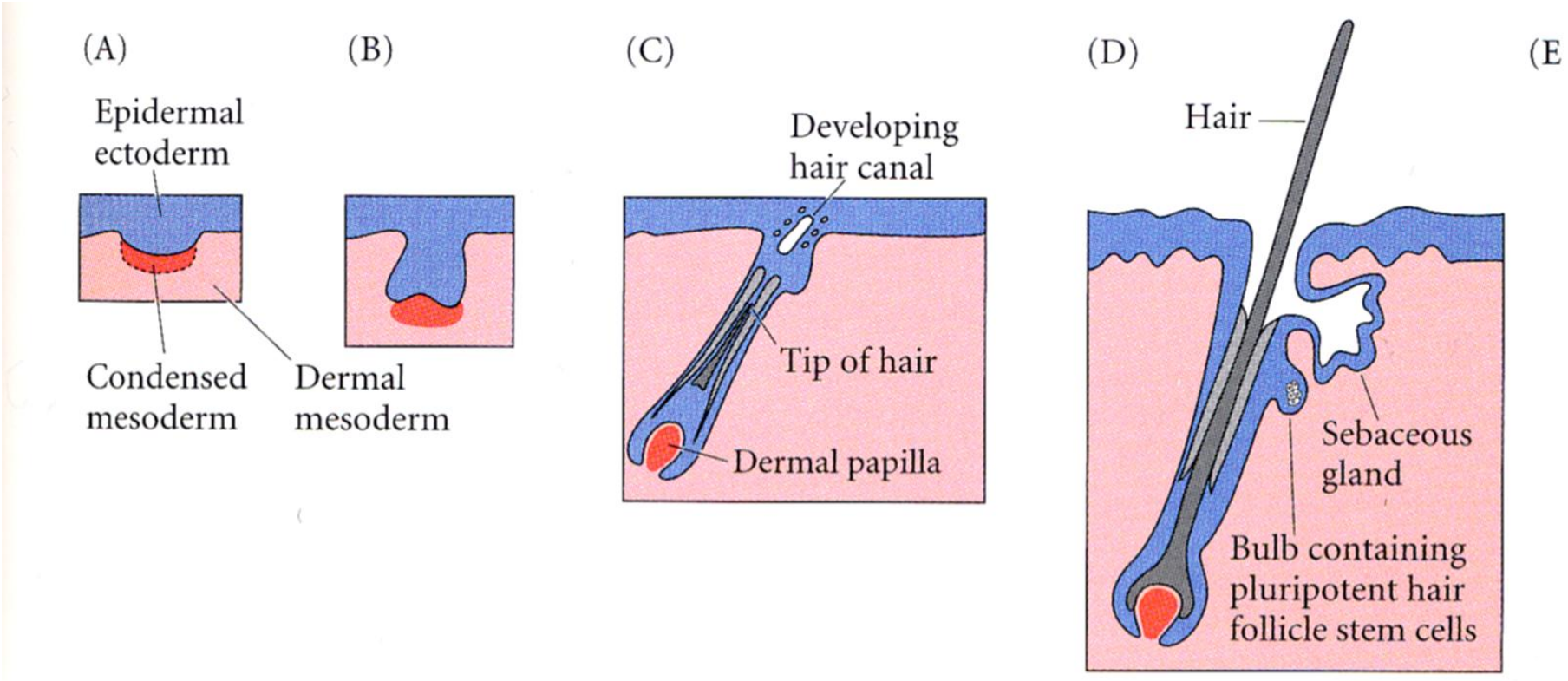


(a) Puppy



(b) Adult dog

Hair formation



12 SEPTEMBER 2008 VOL 321 SCIENCE www.sciencemag.org

BREVIA

A Mutation in Hairless Dogs Implicates *FOXI3* in Ectodermal Development

Cord Drögemüller,[1] Elinor K. Karlsson,[2] Marjo K. Hytönen,[3,4] Michele Perloski,[2] Gaudenz Dolf,[1] Kirsi Sainio,[3] Hannes Lohi,[4] Kerstin Lindblad-Toh,[2,5] Tosso Leeb[1]*

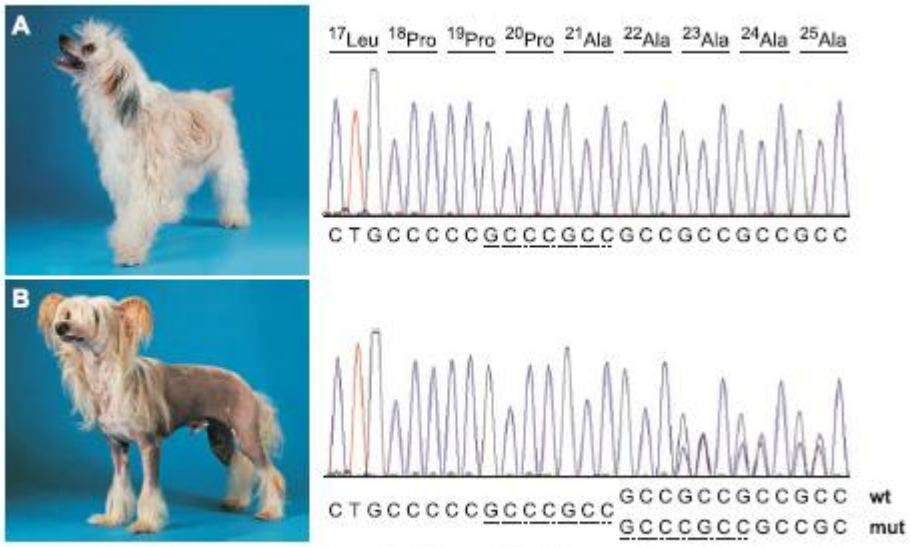
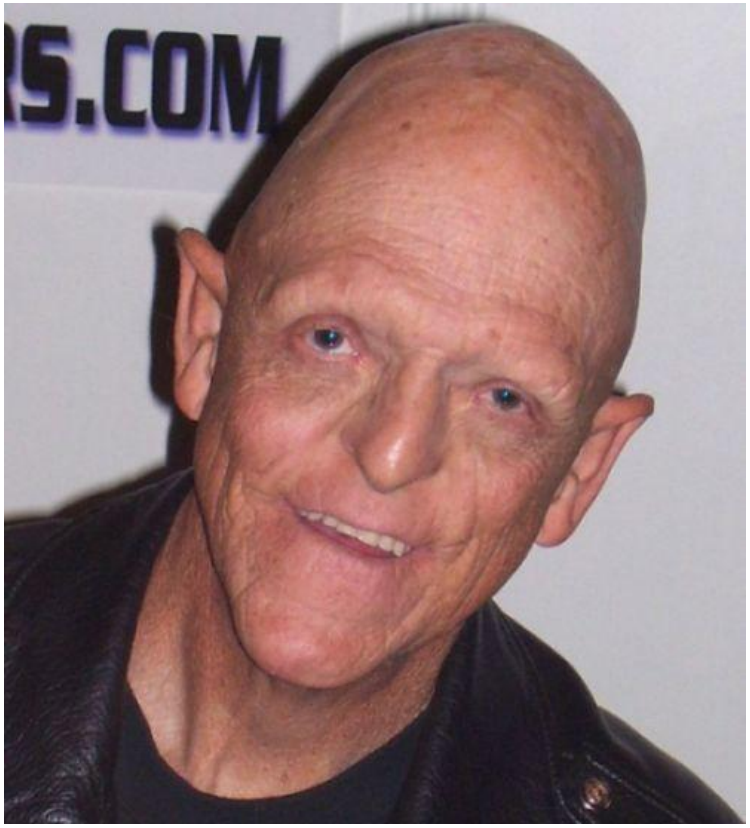


Fig. 1. Phenotype and *FOXI3* sequences of a (**A**) coated (wild-type, wt) or (**B**) hairless Chinese crested (mut) dog. Hairless dogs have a 7-bp duplication (underlined) in exon 1 of *FOXI3* (c.57_63dup7).

Hairless Mutation

- Hairy individuals are normal wild type dogs
- Dogs with single mutation allele are hairless
- Homozygotes die during embryogenesis (semi-lethal gene)

Ectodermal dysplasias in humans



Colours in dogs

Hair colours

- **Hair colour** is the pigmentation of hair follicles due to two types of melanin, eumelanin (black and brown shades) and pheomelanin (red shades)
- All other colours in dogs are mixtures of these two, also the AMOUNT of the pigment affects the colour (black vs. grey)
- WHITE is not a colour, it is lack of pigmentation!

Colour alleles

- A (agouti) = agouti signalling protein (ASIP) = the wolf colour
  - a^y = fawn (cream to yellow to red with darker tips) sable (some solid black hairs intermingled amongst reddish hairs)
  - a^w = wild color of sable (black tips on cream to red hairs)
  - a^t = black-and-tan or brown-and-tan
  - a = recessive black

Colour alleles

- B (brown) = tyrosinase related protein 1 (TYRP1)
  - *B* = black eumelanin
  - *b*, including (b^s,b^d,b^c) = brown eumelanin

Colour alleles

- D (dilutes or pales eumelanin pigment to blue, and pheomelanin subtly) = melanophilin protein MLPH
  - *D* = not diluted – no melanophilin
  - *d* = diluted pigmentation – melanophilin produced in the hair

Colour alleles

- K (from black, "dominant black") = Beta-defensin 103
  - K^{B} = solid black, brown or blue (eumelanin pigmentation only)
  - k^{br} = brindle (on body region that would be phaeomelanin pigmented otherwise)
  - k^{y} = makes the expression of recessive agouti alleles possible

Colour alleles

- M (Merle) = (SILV)
  - *M* = Merle apparent on dogs that are not *e/e*
  - *m* = wild type, no merle mutation
- H (Harlequin) = for the Harlequin pattern to occur, at least one H allele and one M allele must be present.
  - *H* = Harlequin pattern of Great Danes
  - *h* = wild type, no Harlequin pattern

Colour alleles

- S (Spotting) = microphtalmia associated transcription factor MITF (several alleles)
  - *S* = Solid, or more correctly, minimal to no white markings
  - *s* = piebald or randmon spotting, also called particolor

Mendelian inheritance of colours

Bb Dd

Bb Dd

B- D-

bb D-

B- dd

B- dd

B- dd

bb dd

B- D-

B- D-

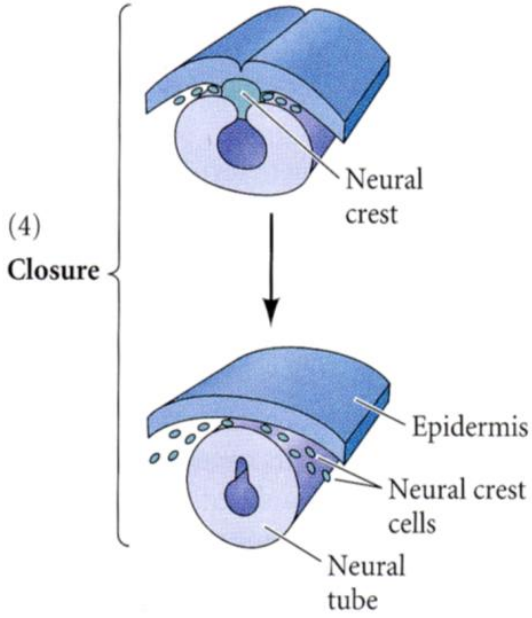
B- D-

Genotypes?

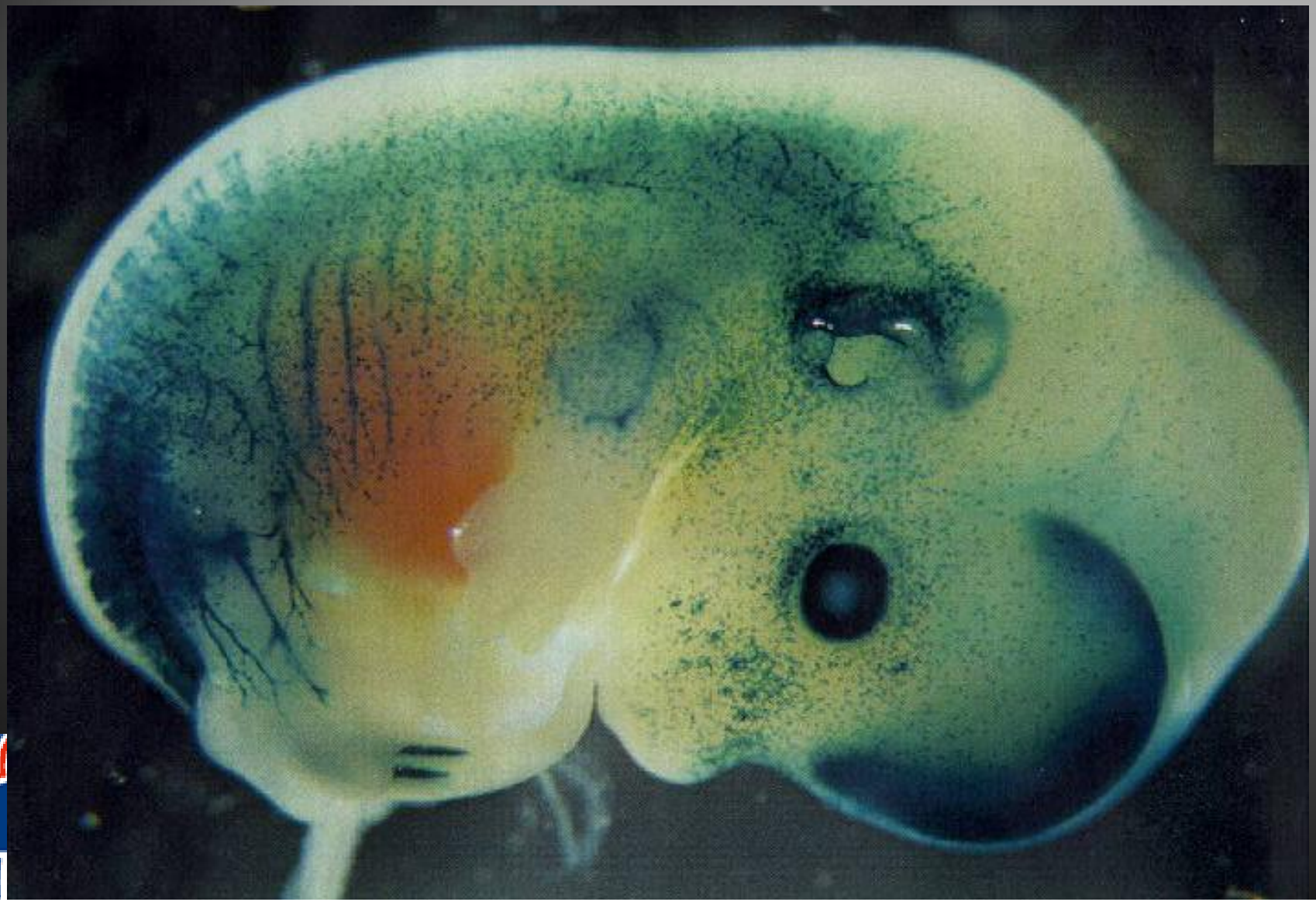
Why colours may cause problems?

Melanocytes produce pigmentation

- Melanocytes are derived from the neural crest
- Many of the proteins that affect pigmentation have some other function in other neural crest-derived tissues, such as the peripheral nervous system



Migration of melanocytes



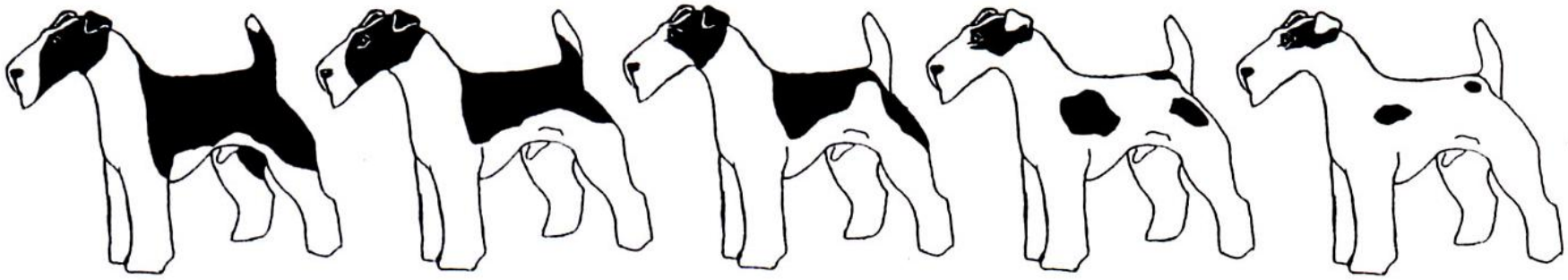
Piebaldism

- White spotting alleles in dogs are recessively inherited
- White spotting-genes s^p ja s^w
- Piebald = “magpie” + “bald eagle”
- White spotting is caused by the lack of melanocytes in areas of skin

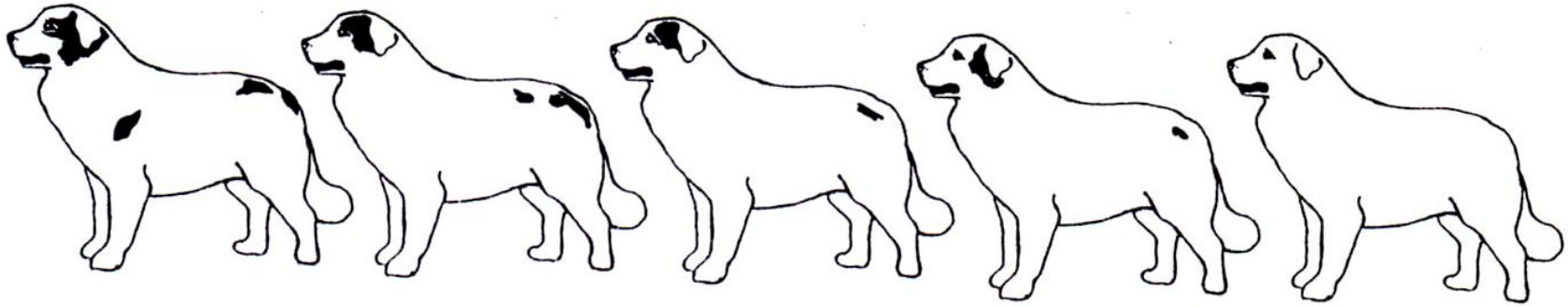
Piebaldism

- The amount of white colour depends also on modifiers, such as the Merle-gene
- s^{i} Irish Spotting , white markings on head, feet, tail, chest, neck
- s^{p}, 'piebald", white markings cross the back (SINE mutation on MITF)
- s^{w}, 'extreme white piebald'
- 'colour headed' ($s^{p}s^{p}$, $s^{w}s^{w}$)
- Dogs that are extremely white, can also be deaf

Piebaldismi koiralla



PLUS MODIFIERS MINUS



PLUS MODIFIERS MINUS

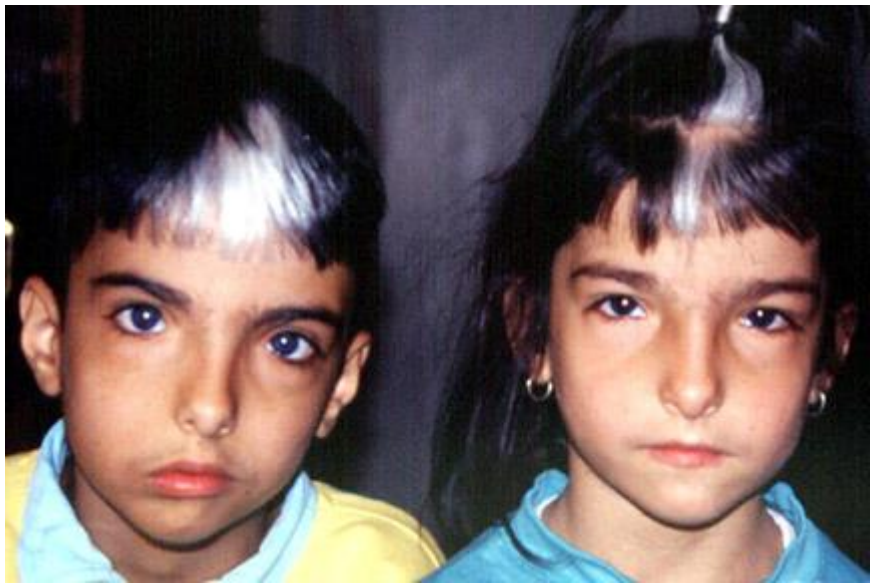
By genotyping ten white (s^w/s^w; **Supplementary Fig. 3a**) and nine solid (*S/S*; **Supplementary Fig. 3c**) boxers, we mapped s^w to an associated region of less than 1 Mb containing only one gene: *microphthalmia-associated transcription factor* (*MITF*). The most strongly associated SNP ($P_{raw} = 7.1 \times 10^{-10}$, $P_{genome} = 3 \times 10^{-5}$) lies within a haplotype of 800-kb defined by 11 SNPs ($P_{raw} = 1.4 \times 10^{-8}$, $P_{chr} = 4.0 \times 10^{-5}$) that is homozygous in all white boxers and absent from solid dogs (**Fig. 2b,d**). The predominant haplotype in solid boxers has a frequency of 78%, and several minor haplotypes are also present. The sequenced boxer, with intermediate 'flash' pigmentation, is heterozygous for the white haplotype and the predominant solid haplotype. The association is 1,000-fold stronger than any other region in the genome.

MITF is an important developmental gene with a complex regulation implicated in pigmentary and auditory disorders in humans and mice[19–21]. *MITF* is thus an ideal candidate locus for s^w, which affects both pigmentation and hearing.


Coastal
White German Shepherd Dog

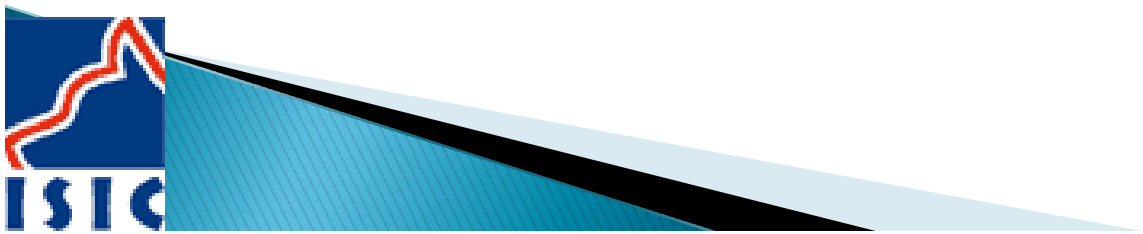
Do we have colour genes?

- YES!!
- Human also have disorders, such as the Waardenburg syndrome that cause 2-5 % congenital deafness world wide

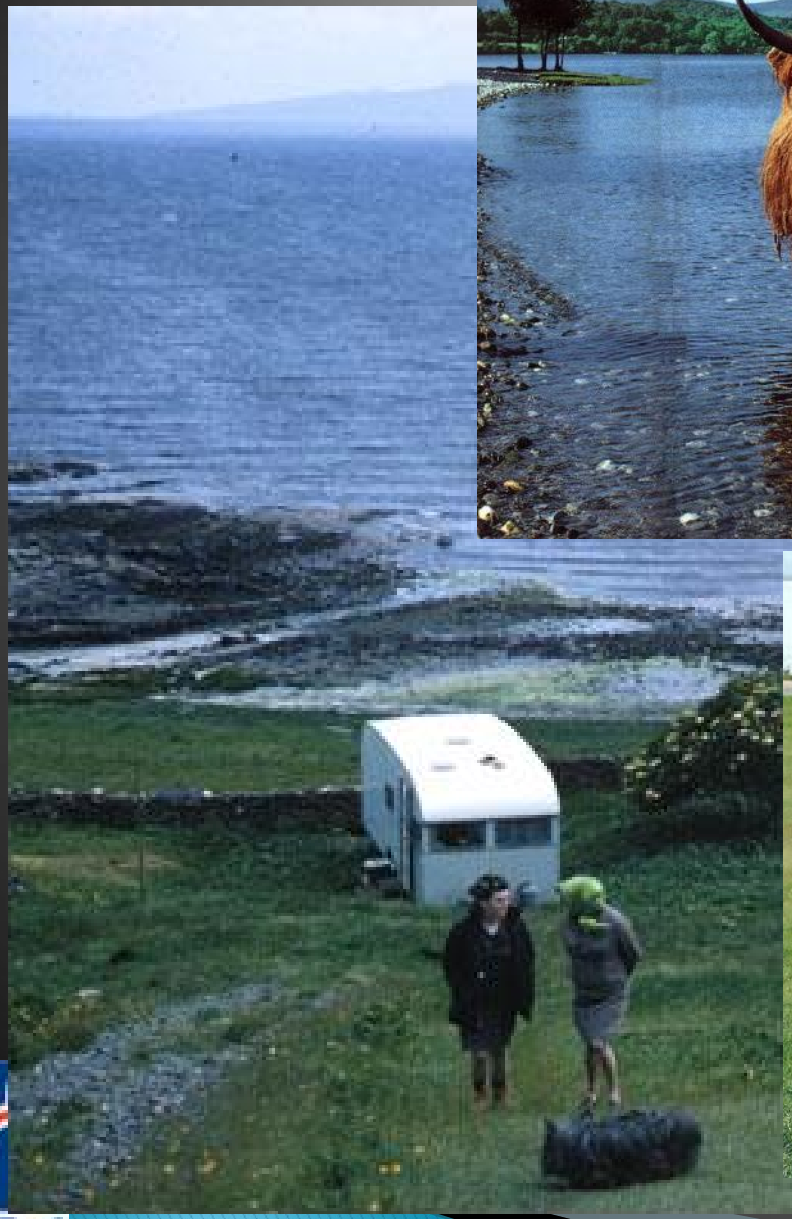


- Waardenburg syndrome a rare genetic disorder most often characterized by varying degrees of deafness, other defects in structures arising from the neural crest, and pigmentation anomalies.
- Type IIa, WS2A caused by a mutation in human MITF gene

Diseases in breeding



What should we know about our own breed ?




706

Should we breed diseases or a dog?

- Sometimes it seems that the diseases are more important than the dog – so who is actually wagging the tail of the dog?
- Why do we end up with breeds with so many inherited disorders that we cannot find anymore a healthy individual that we could breed from?

What is not normal?

- That the dog is constantly itchy
- That the dog is in lame
- That the dog does not hear
- That the dog does not see
- That the dog cannot move
- That the dog cannot live without a special diet
- That the dog dies before the age of 6
- That the dog cannot reproduce without assistance
- That the dog is bad tempered

What are inherited diseases?

- ***Congenital*** – visible at the time of the birth or in young individuals
- ***progressive*** – later onset – f.ex hereditary cataract
- ***Congenital and progressive diseases*** – f.ex. idiopathic epilepsy

Terminology

- ***Malformation:*** congenital, but sometime are visible later in life – f.ex. kincky tail can ”appear” only after the development of the bony structures (vertebrae) is well on its way
- ***Syndrome:*** several malformations or symptoms occur simultaneously or are connected to each other – may differ between individuals
- ***Association:*** several different symptoms occur statistically more frequently together, the variability however is great
- ***Sequence:*** malformation or symptom that is a consequence from some other condition

Terminology

- ***Aplasia:*** the organ is missing
- ***Dysplasia:*** the organ or structure has abnormal appearance – can be either congenital or progressive
- ***Hypoplasia:*** the organ has not fully developed

Problems in Icelandic Sheep Dogs?

- Hip dysplasia
- Hereditary cataract
- RD (multifocal?)
- Distichiasis
- ***Cryptorchism***
- Hypodontia
- Renal dysplasia or familiar nephropathy
- ”Näsmjölk”
- Others?


Finally!
Thank you!