Actual challenges in breeding show type Greyhounds

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Greyhound Hereditary Neuropathy

(also: Hereditary Polyneuropathy)

Onset: 3 – 9 months of age

Generalized muscle weakness

Exercise intolerance

„bunny-hopping“ gait

Absence of reflexes

Laryngeal affection: changes in voice, regurgitation

Final stage: severe ataxia, muscle atrophy, inability to stand

No pain! general condition not affected!

Greyhound Hereditary Neuropathy

cause: missense mutation in the *NDRG1*-gene

- Undersupply of the peripheric nerve system, leading to nerve degeneration
- Due to the lack of nervous stimulation the muscles degrade gradually
- recessive inheritance
- Resembles human Charcot-Marie-Tooth-Disease type 4D

DNA test available since 2009

What we have learnt from Neuropathy…

NOTHING!

- Matador breeding continues
- Breeding programmes all over the world are more and more based on the same dogs
- Unfashionable bloodlines disappear
- Impoverishment of the gene pool is rather accelerated
- Neuropathy was a „warning shot“, which went unheard
- **If we don‘t change our breeding strategies, it‘s not the question IF we will face a new recessive disease - but only which one and when…**

Spinal cysts - Symptoms and clinical signs

- typical symptoms: scratching the neck and biting in the legs, sometimes screaming from pain – similar to Syringomyelia in Cavalier King Charles Spaniels
- resembles „phantom pain“ in neck and legs
- varying from mild single episodes (sometimes only a few times in whole life) to severe scratching/biting episodes combined with gait abnormalities and ataxia
- blood examination: normal parameters
- MRI: abnormal fluid accumulation in the central nerve system, either in the brain stem or cysts in the spinal cord, mainly in the neck (C2/3 up to C6/7)

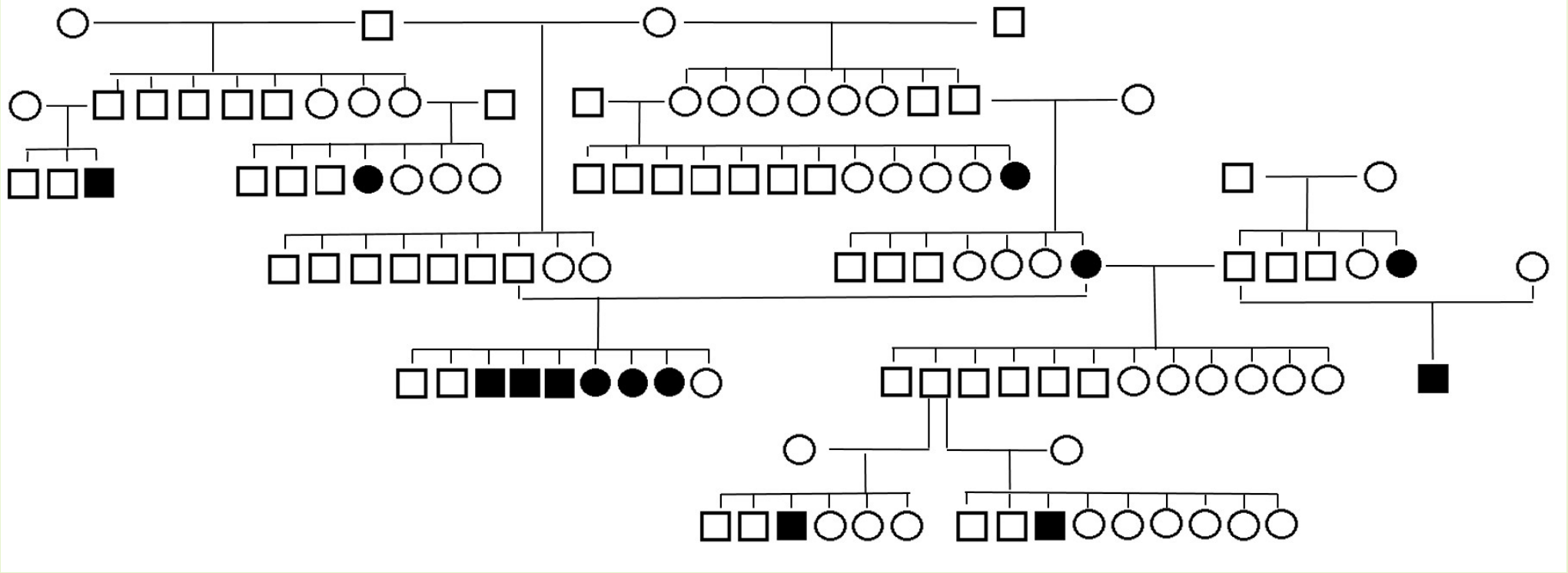
What we know

- 19 dogs with typical symptoms
- in 5 of them diagnosis confirmed by MRI
- one more case verified by autopsy
- 5 dogs have been euthanized due to severity of symptoms in young age (1,5 to 3 years)
- others had/have a normal lifespan with single mild episodes only

What we don‘t know…

- How do these cysts occur
- Mode of inheritance
- therapy?

Pedigree analysis



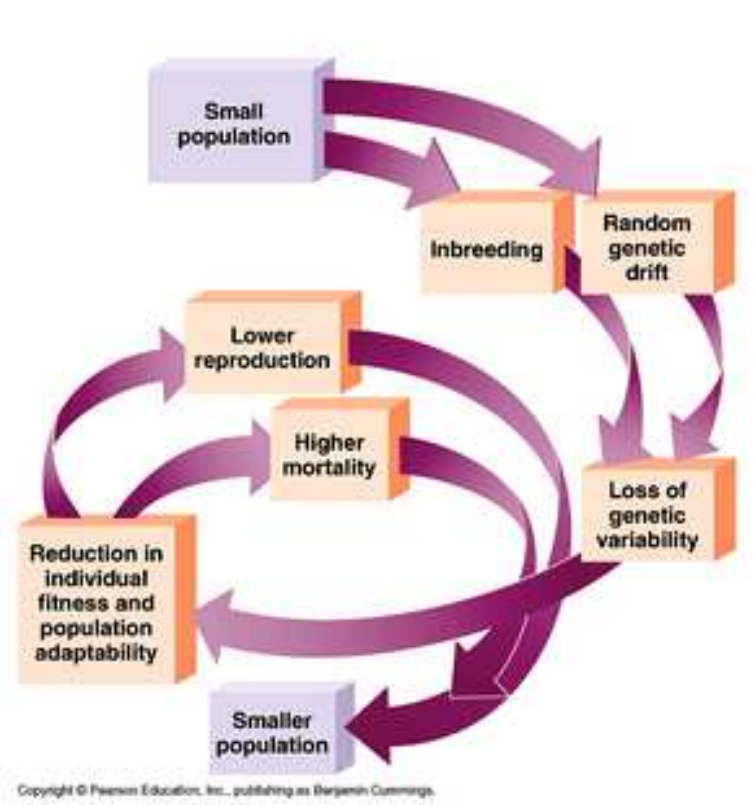
Hypothesis

- Mode of inheritance most likely *not* recessive
  → in 2 cases affected dogs originate from nearly outcross matings (one of them MRI confirmed)
  → for a recessive trait I would expect more cases from more different kennels
- probably dominant with incomplete penetrance
  → size and localization of cysts might influence severity of symptoms
  → dogs with very small cysts might have no problems at all and appear healthy
- or caused by specific physiognomy?
  → narrow skulls could lead to a liquor circulation blockade
  not really likely…

What has been done until now?

- blood/DNA samples collected at the University of Berne/CH
- Funding for clinical and MRI examination coordinated by the Faculty of Veterinary Medicine in Oslo
  chief neurologist: Karin Hultin Jâderlund
  karinhultin.jaderlund@nmbu.no
- neuropathological examination:
  Kaspar Matiasek, Munich
  kaspar.matiasek@neuropathologie.de

How to break the vicious cycle?



Homozygousity (I)

Definition: both alleles on a gene locus are identical

Natural situation:

- Homozygousity is highly undesirable
- Variation in alleles is essential for the adaptability of an organism (or a population) on environmental conditions
- Strong mechanisms to avoid inbreeding
  → homozygousity for mutations is a very unlikely event in wild populations

Homozygousity (II)

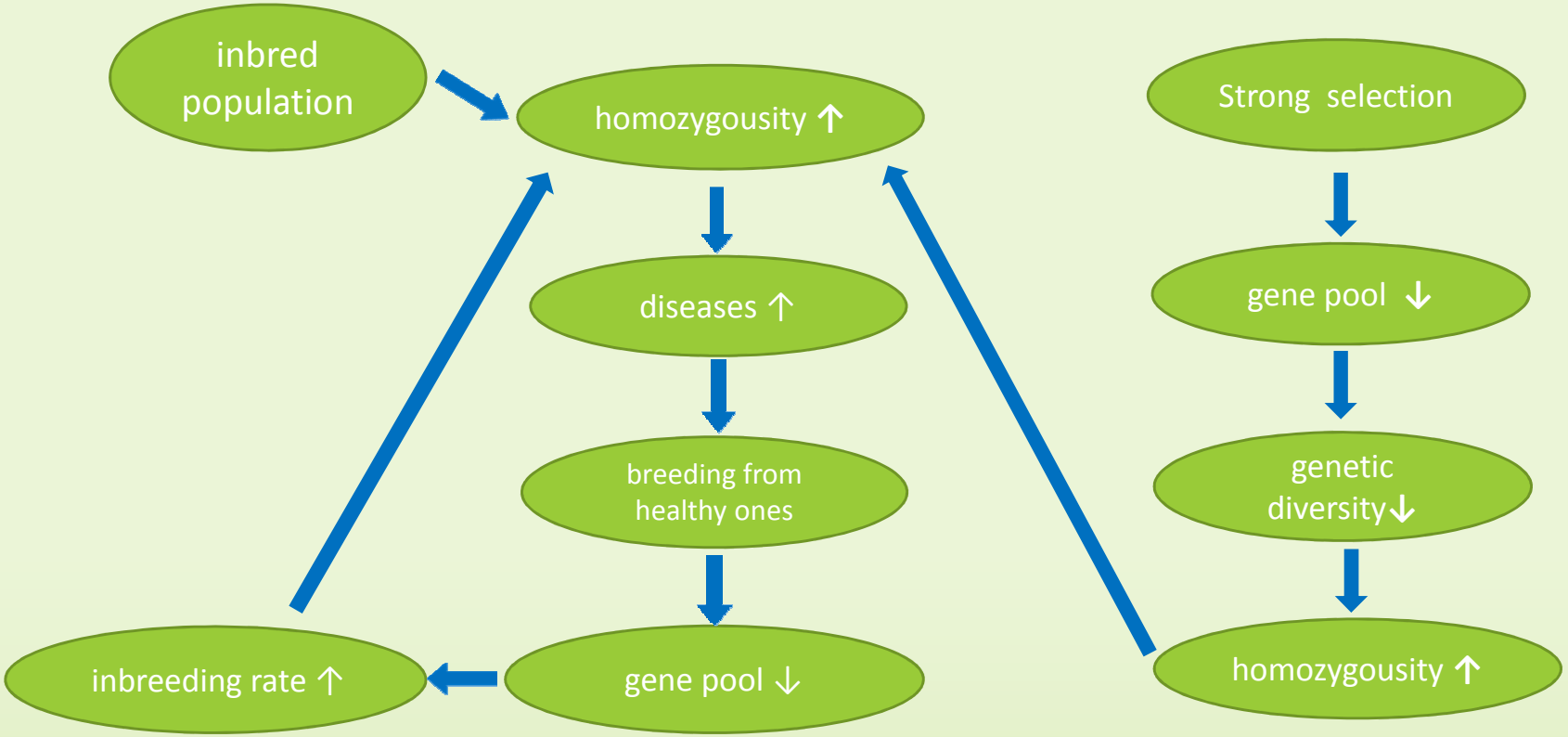
Artificial selection:

- Targeted inbreeding is a widely used selection tool to archieve homozygousity for desired traits
- The more homozygous an animal, the more reliably it will inherit his characteristic traits to its offspring
- Inbreeding increases the probability to produce offspring with certain desired traits, **but increases also the risk that undesired traits (mutations) are doubled up!**

Mutations

- Caused by faults in DNA replication
- **Every living creature carries a load of several recessive mutations** – most of them unknown
- One intact allele is usually sufficient and can maintain function
- Recessive mutations only become visible if an individual has two defective alleles, inherited from each of the parents

How to ruin a breed…



Why do genetic diseases occur?

- The occurrence of Neuropathy or the „new neurologic disease“ (spinal cysts) was neither bad luck, nor coincidence, nor the fault of a certain dog (or certain breeder) –
  it was the direct consequence of of the way the Show Greyhound population has been developed in the last decades!
- **It‘s the price we have to pay for even, typey litters of predictable Champion quality…**

More risks - DLA-Haplotypes

- DLA-complex: Group of genes, responsible for a part of the immune system (discrimination between endogenuous and exogenuous antigens)
- maximal diversity on these gene loci is essential to maintain function
- DLA genes are often inherited „en bloc“ = haplotype

DLA-Haplotypes

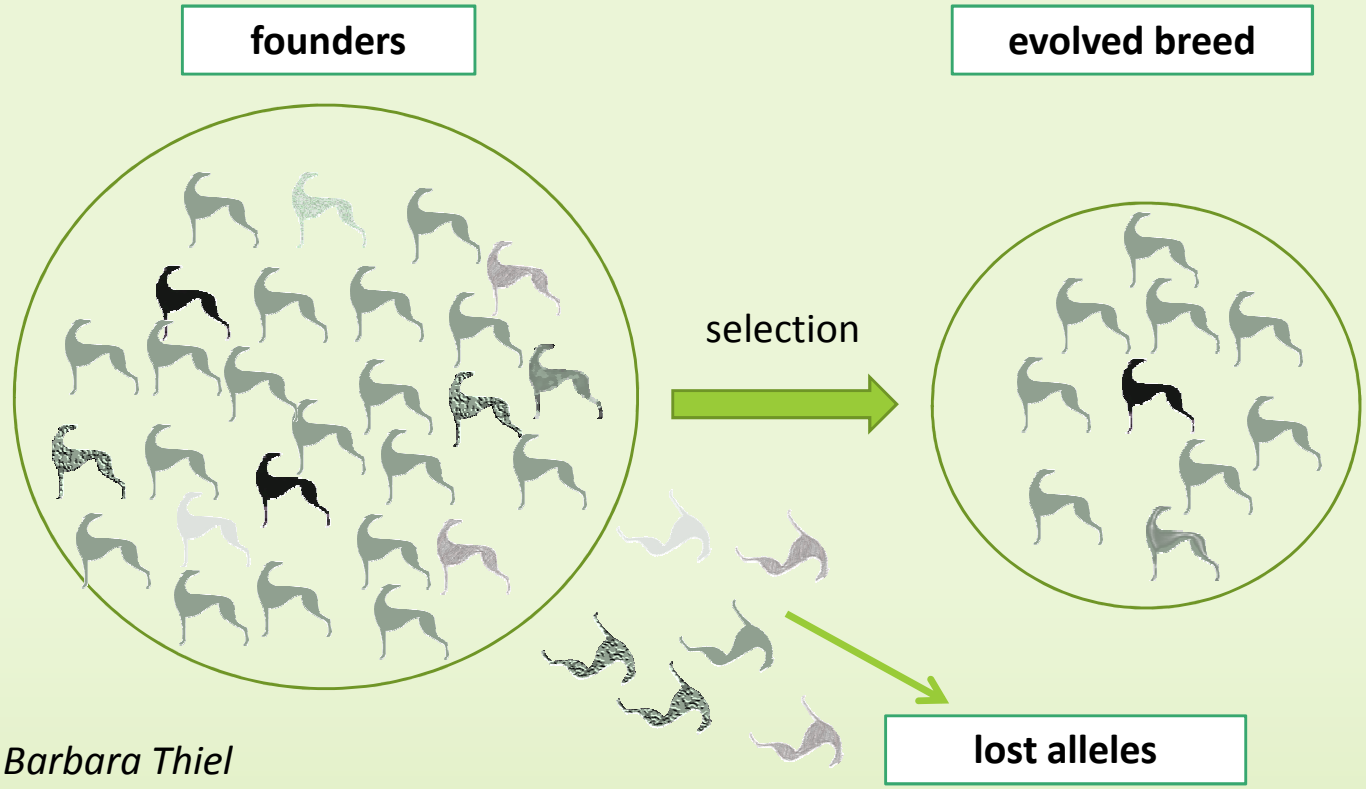
- about 170 DLA-haplotypes are known in dogs
- in separate breeds, variability is strongly reduced (often less than 20)
- in several breeds, a correlation of certain DLA haplotypes to varying autoimmune diseases is proven
- risk even increasing if haplotypes are homozygous

DLA-Haplotypes

Autoimmune diseases associated with reduced DLA-variability:

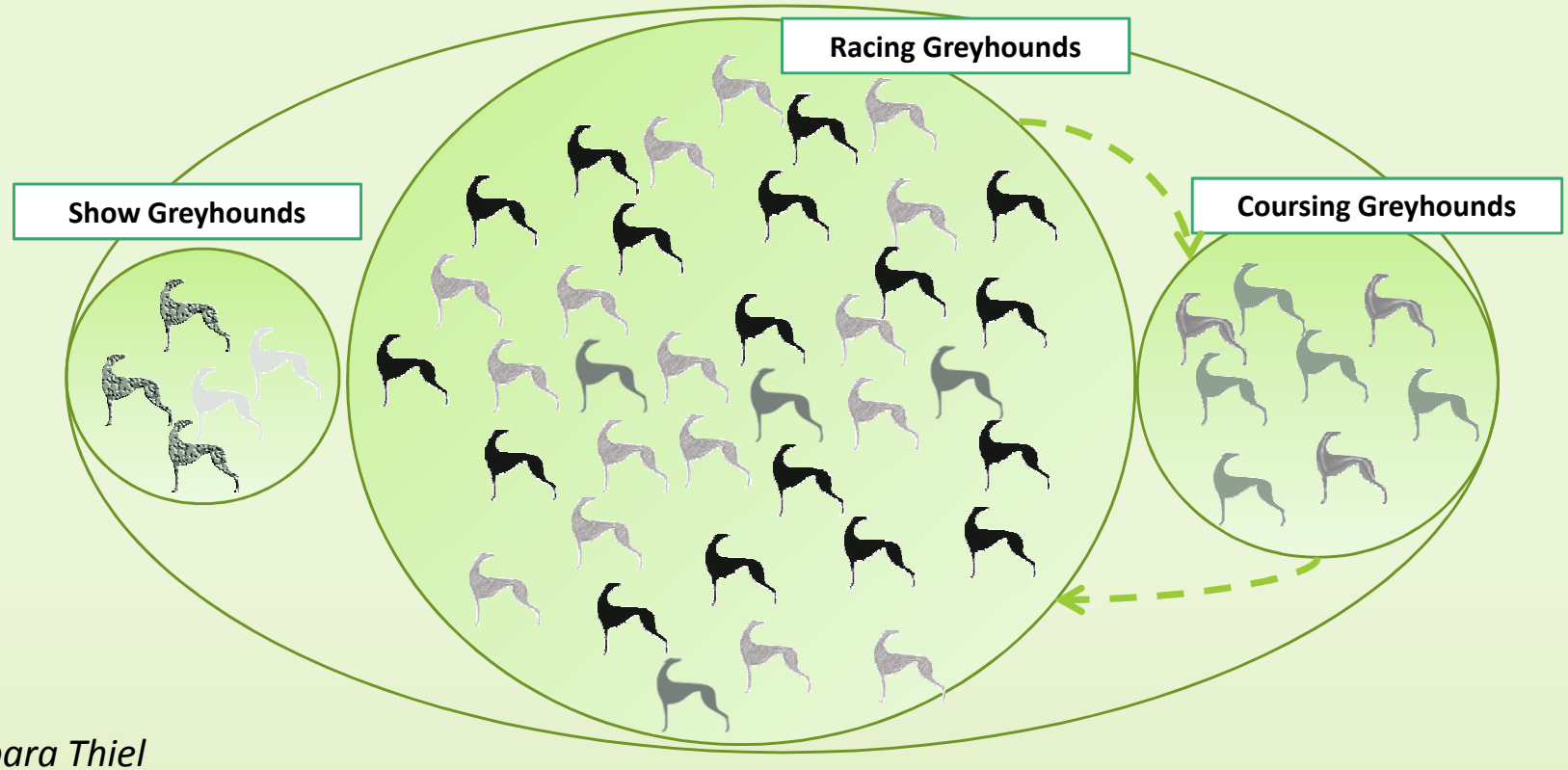
- Food allergies
- Diabetes
- Morbus Addison
- AIHA (autoimmunohemolytic anemia)
- immune-mediated rheuma
- SLO (symmetric lupoid onychodystrophy)
- Hypothyreoidism
- Enzephalitis, Meningitis

Breed formation



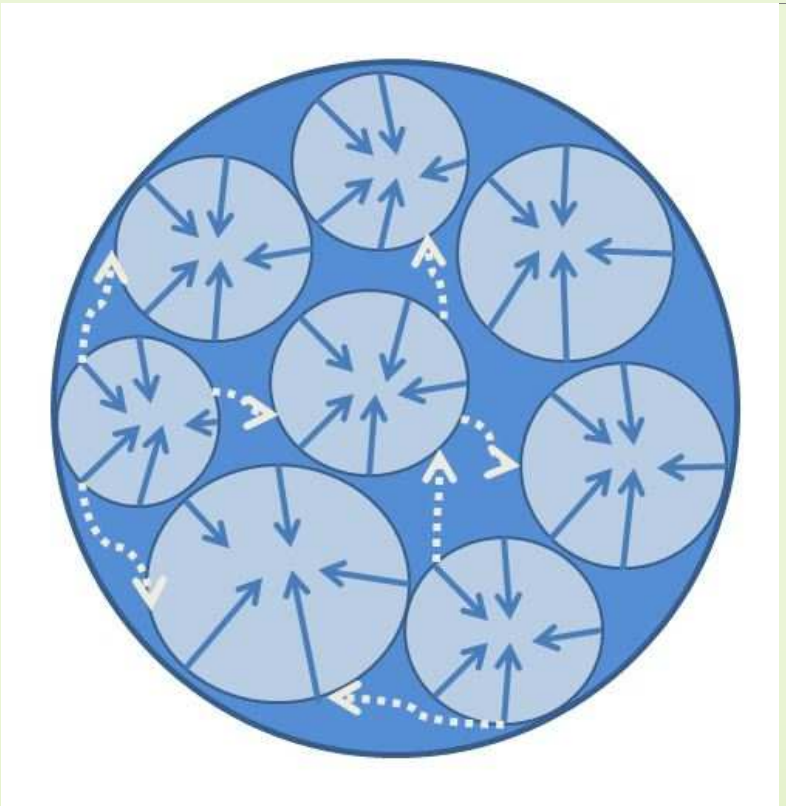
Graphics: Barbara Thiel

Unique Situation in Greyhounds



graphics: Barbara Thiel

Breeding 50 years ago



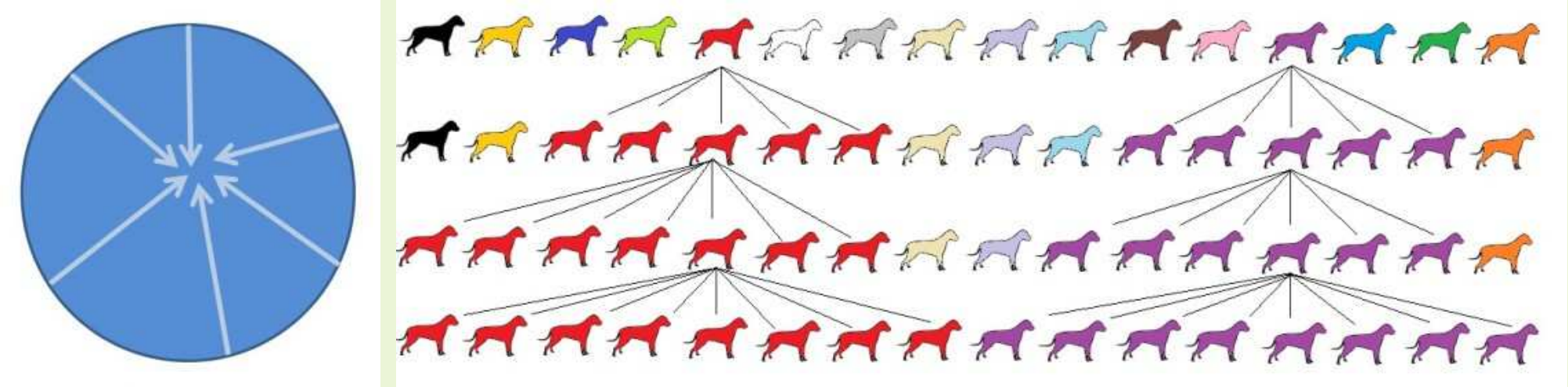
- Several kennels fixed their own kennel type by line- and inbreeding

→ several inbred, but separated populations
→ genetic diversity of the breed in total was preserved
→ outcross to an unrelated population was always possible

- **Balance between inbreeding and outcrossing**

graphics: Barbara Thiel

Problems started here…



graphics: Barbara Thiel / feragen

In the last decades, breeding was more and more focused on a few topwinning lines only – lines out of fashion get lost irrevocably.

Actual state of the Show Greyhound population

- Do we have a matador problem?
- Is the gene pool of the Show Greyhound *really* that small?

A summary of Show Greyhound Breeding 2014 - 2018

WORLDWIDE		EUROPE	
Litters :	235	Litters:	172
average/year:	47	average/year:	34,4
Puppies:	1418	Puppies:	1182
average/year:	283,6	average/year:	236,4

Data collected from www.greyhound.breedarchive.com, only show type and half&half litters

Influential Sires

4 BEAUTIFUL SIRES WHO CONSTANTLY SIRED TOP QUALITY OFFSPRING

- **Boughton Benvoluto**
  * 11/2000
  6 litters, 37 offspring
- **Epic Brave at Sobers**
  * 10/2001
  6 litters, 50 offspring
- **Epic Bombastic**
  * 10/2001
  3 litters, 26 offspring
- **Showline Sporting Trophy at Sobers**
  * 5/2007
  11 litters, 70 offspring

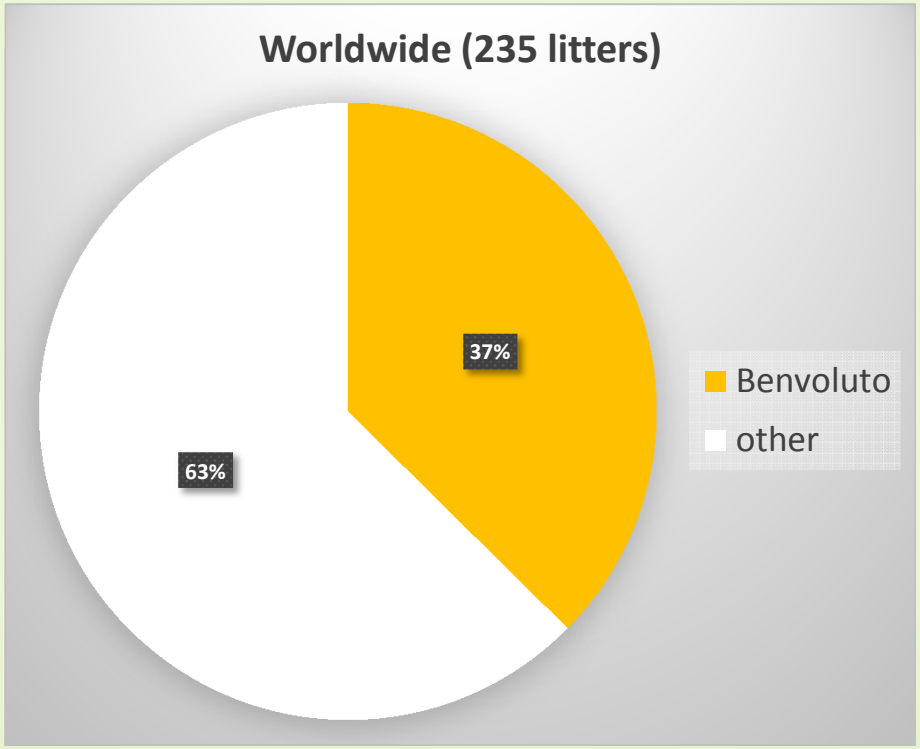
FCI recommendations:

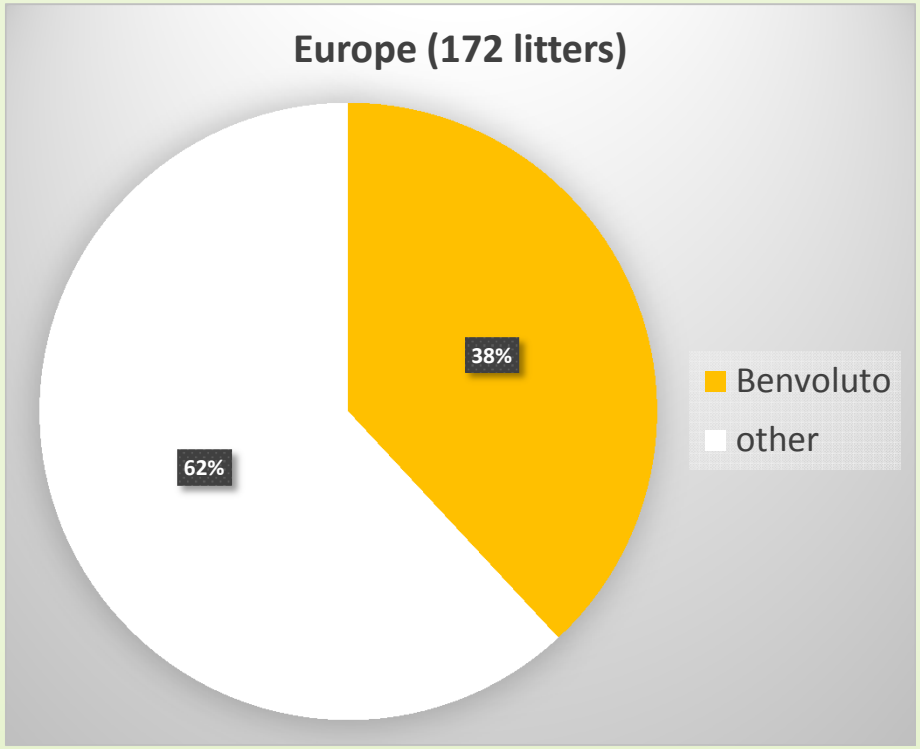
„no dog should have more offspring than equivalent to 5% of the number of puppies registered in the breed population during a five-year period. “

- worldwide 5 %: litters: 11,75%
  puppies: 70,9
- Europe 5%: litters: 8,6%
  puppies: 59,1

Where is the problem?

Blood quota of these sires 2014 - 2018





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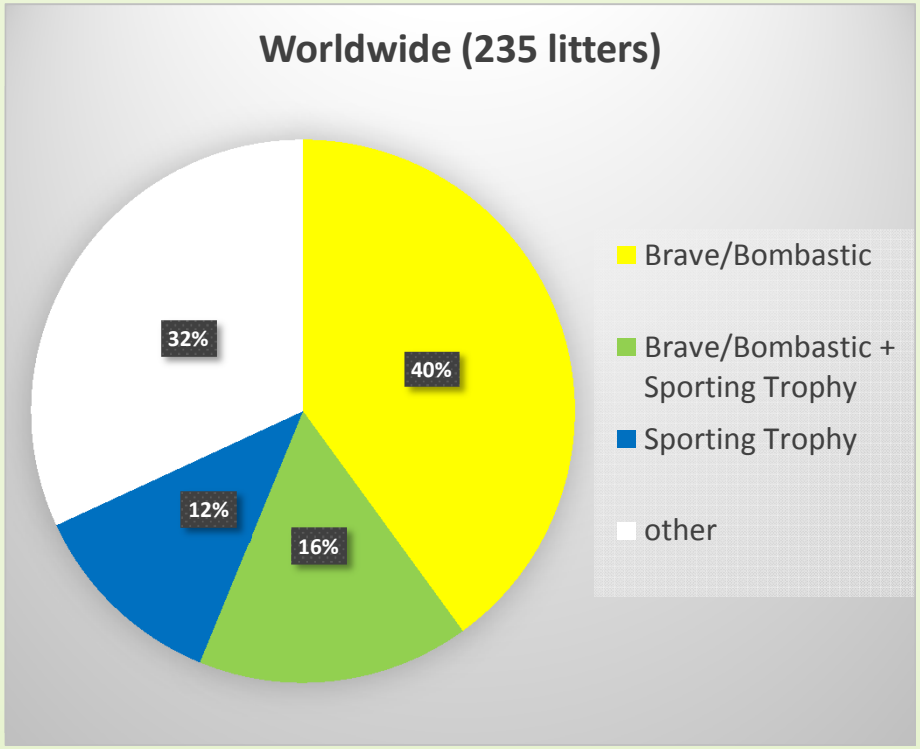

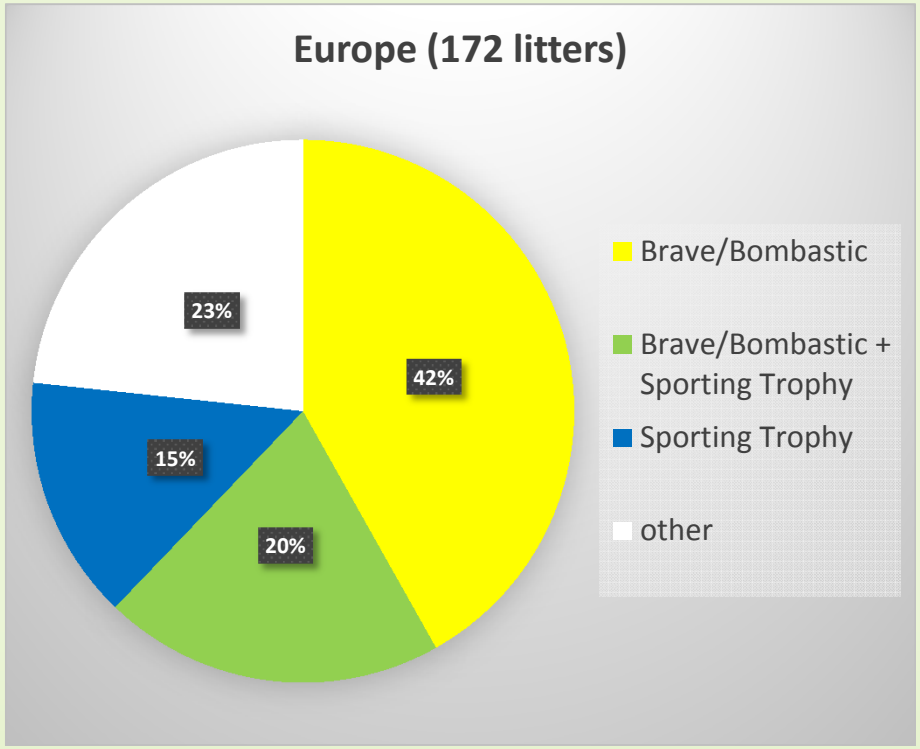

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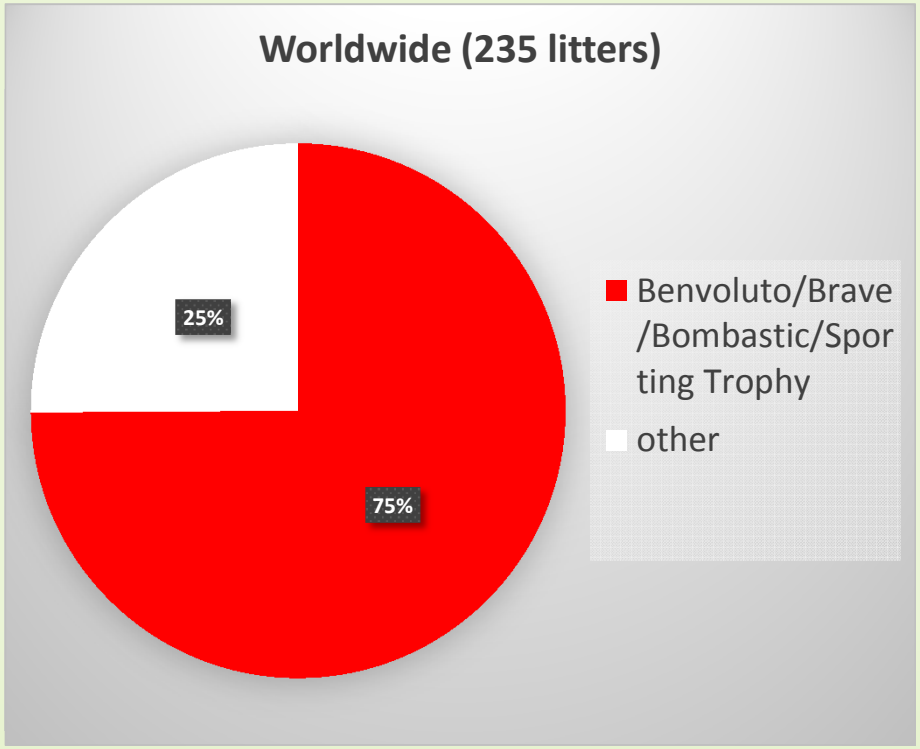
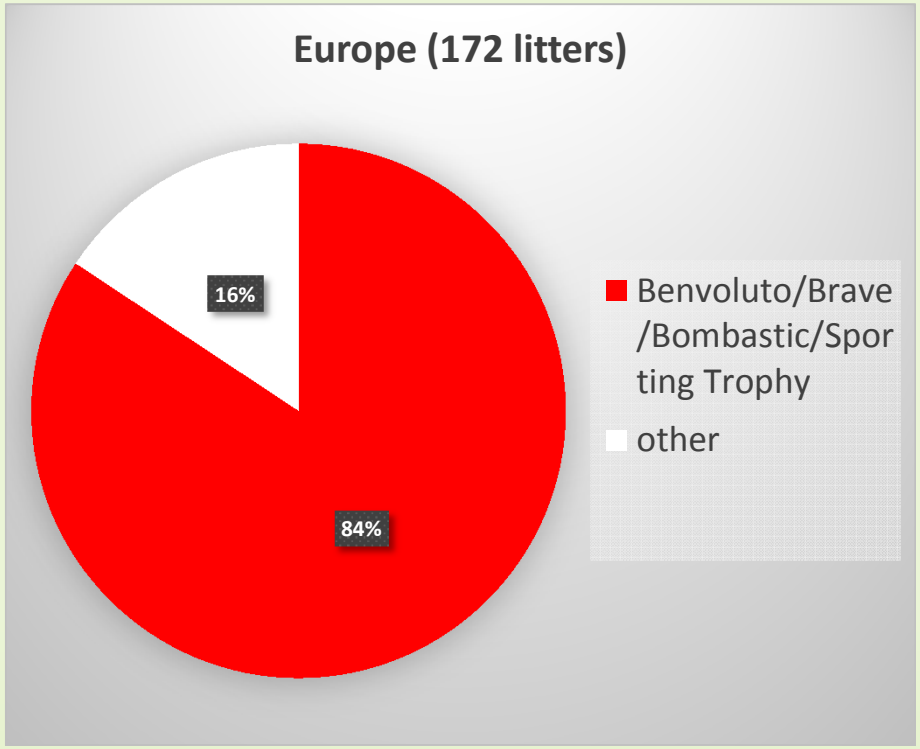




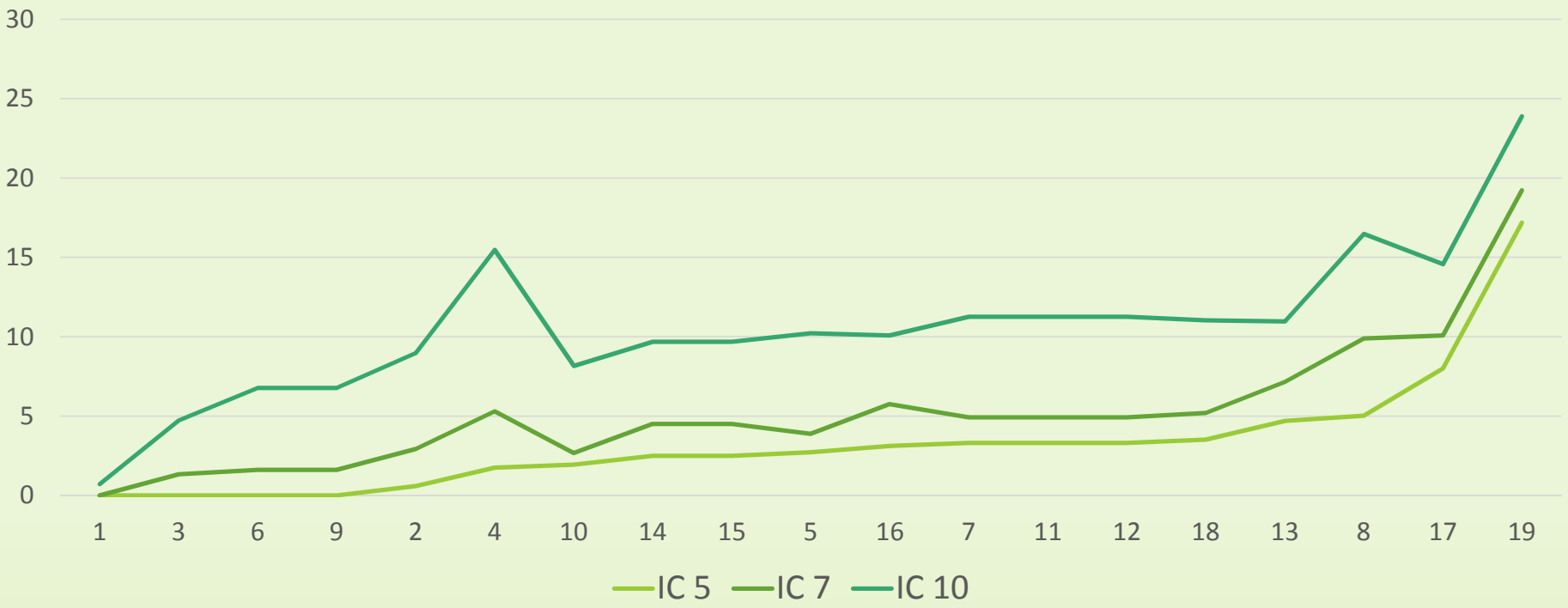
Where is the problem?

- Offspring of these 4 sires is dominating the breeding worldwide (probably we should call it a „**matador line problem**“, not a matador sire problem…)
- 3 of these 4 sires are very closely related
- Only 25% of litters worldwide in this period are free of these sires – still doesn‘t mean that they aren‘t related to them, because they might share ancestors anyway
- main problem: lots of other sires of their generation were excluded from breeding – their genes are lost

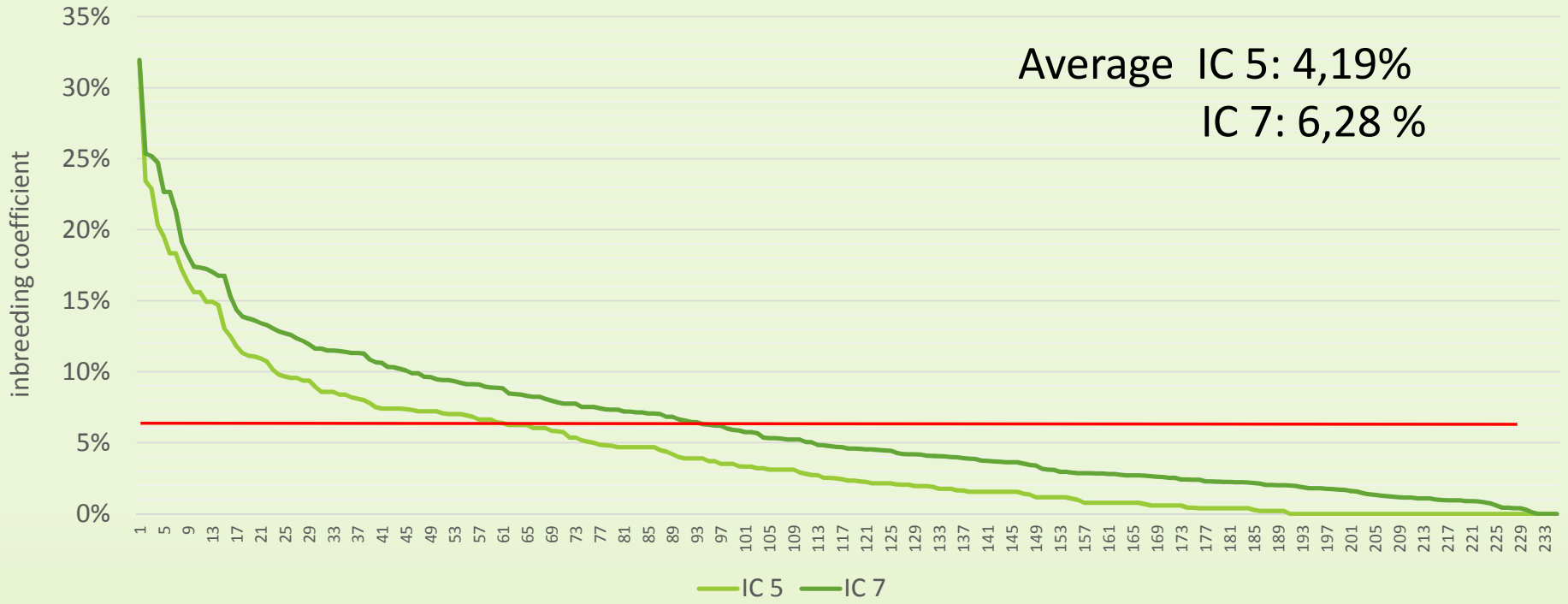
Evaluation of genetic diversity

- **inbreeding coefficient:**
  - probability that two alleles at a given locus are identical by descent
  - percentage of homozygous loci in a dog
- **ancestor loss coefficient:**
  - ratio of the number of unique relatives in a pedigree to the number of possible relatives
  - information about genetic variance
- both coefficients are only comparable if they are based on the same number of generations
- trouble spot: just calculated odds!

Comparison of IC



Inbreeding coefficients 2014 - 2018



red: maximum IC of 6,25% for single matings (Rasspecifik avelsstrategi SvGK / NGK)

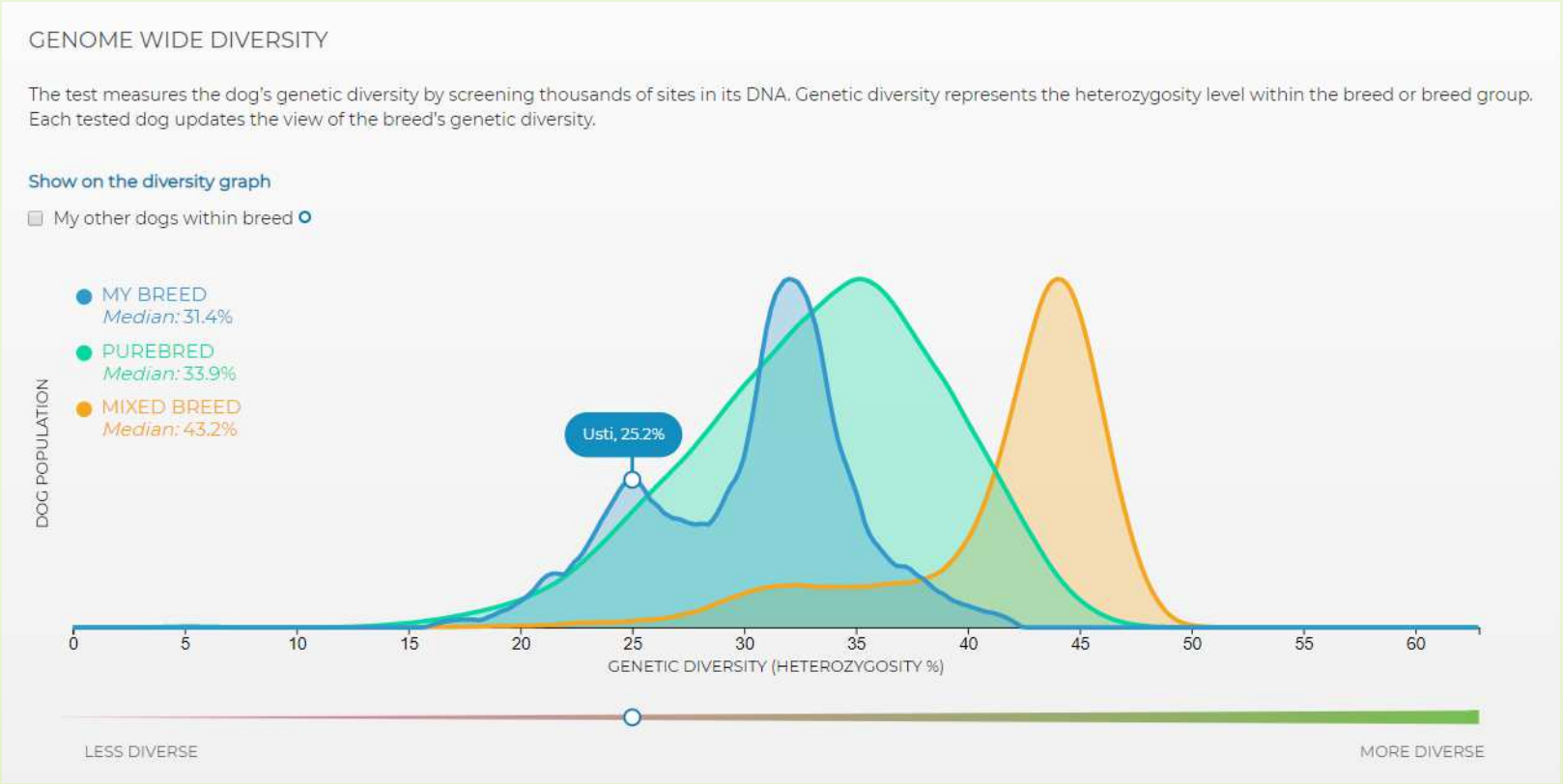
Difficulty of calculated odds

- If a population is intensively inbred since a long time and therefore has a very high level of homozygousity, calculated odds are of very limited validity
- Dogs with very distinct pedigrees (at first glance) still could have common ancestors many generations ago and could share a lot of common alleles

Screening for genomic heterozygousity = „genomic IC“

- DNA-based evaluation of the actual heterozygousity based on thousands of SNP markers
- allows specification of heterozygousity (=ratio of same or different alleles, inherited from father and mother)
- more reliable information than just calculated odds
- by direct comparison of SNP markers of sire and dam, the level of heterozygousity of their prospective offspring can be estimated
- laboratories: mydogdna.com, feragen.at

Heterozygousity graph



- 132 Greyhounds tested
- Median: 31,7 %
- Max: 40,6 %
- Min: 17,6 %

- Median Show: 25,1 %
  (public dogs): 23,7 %
- Median Racing: 32,5 %

A few examples for heterozygousity scans…

Variety among littermates

- Rumford S-litter (IC 7 = 4,93)
  - Silvretta 24,9 %
  - Sovereign 23,9 %
  - Sibelius 23,8 %
- Rumford U-litter (IC 7 = 1,61)
  - Ustinov 25,2 %
  - Ultramarin 24,6 %

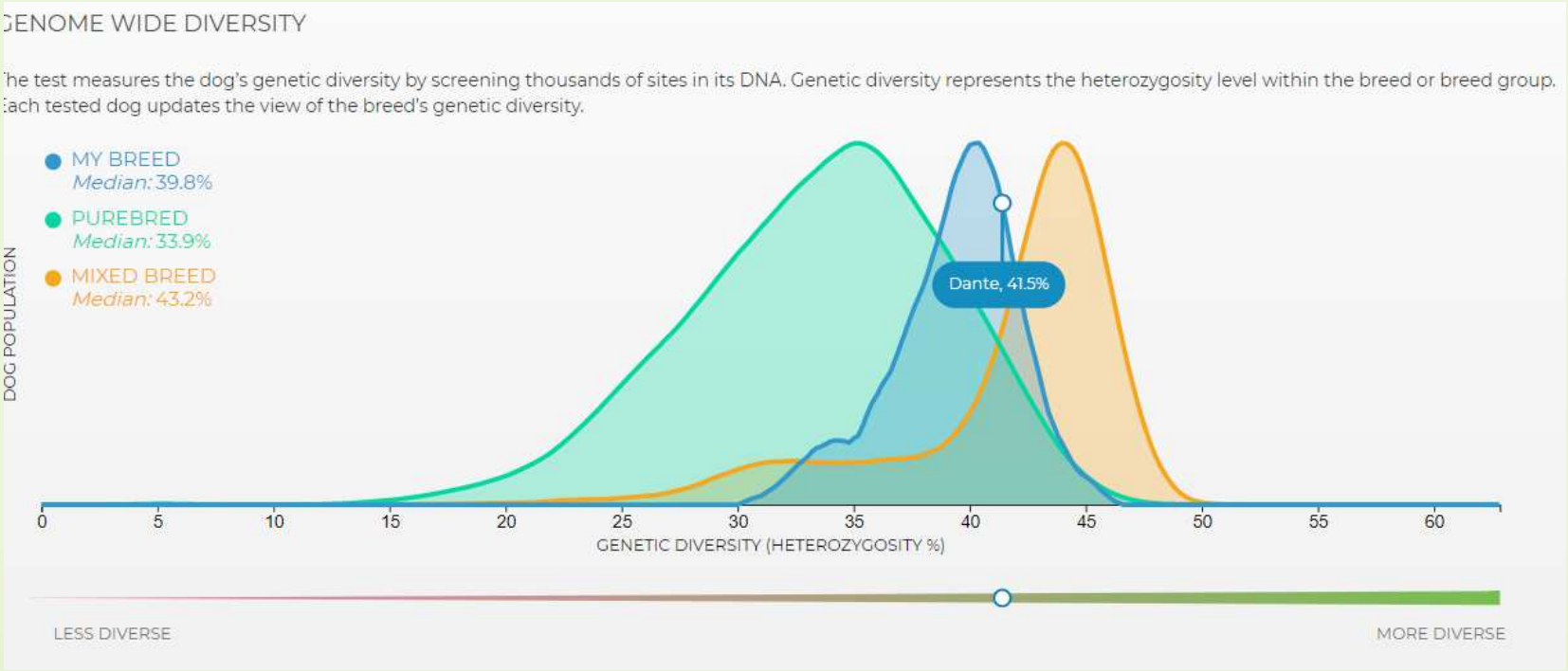
→ IC doesn‘t allow reliable conclusions about the real level of heterozygousity

→ increasing the level of heterozygousity by „outcrossing“ within Show Greyhounds might be impossible (because the whole population is already highly inbred)

Outcrossing to racing lines (1/4 racing, 3/4 show lines)

- Christcile‘s Oguenel 32,4 %

Example from another breed



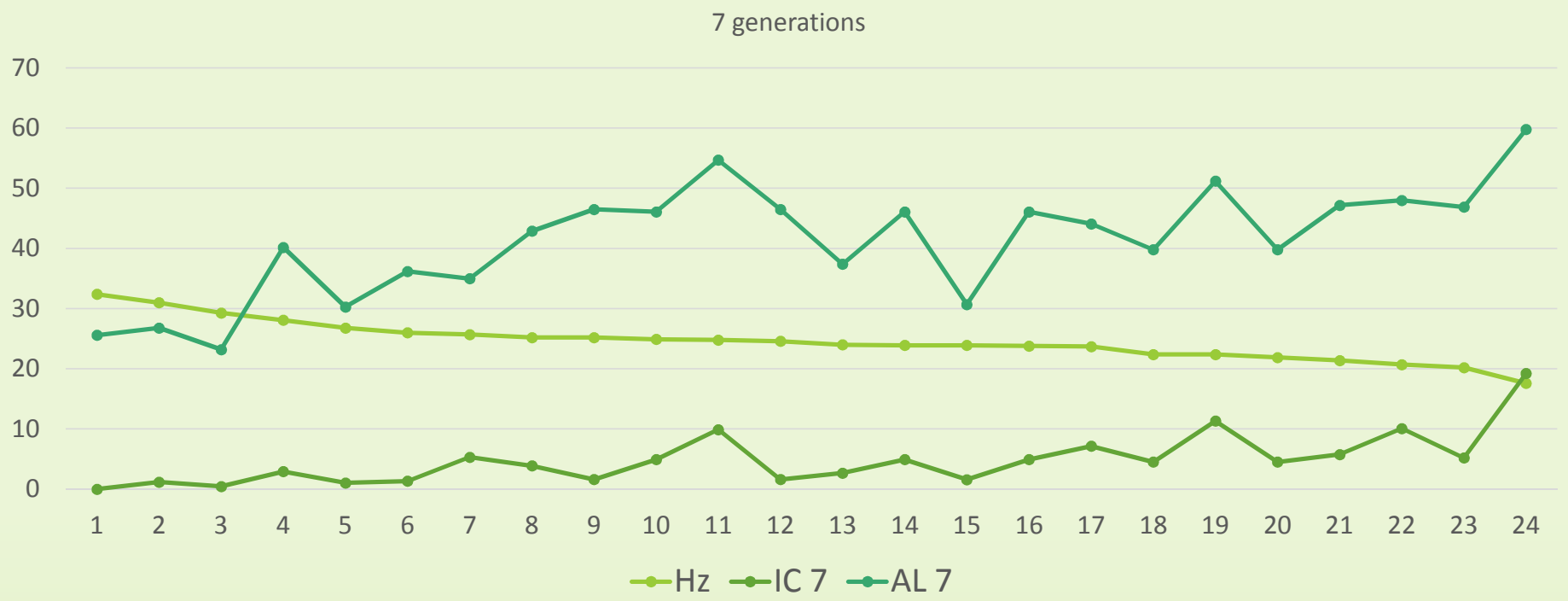
Greyhound „Usti“

- IC 5: 0%
- Hz: 25,2 %

Galgo „Dante“

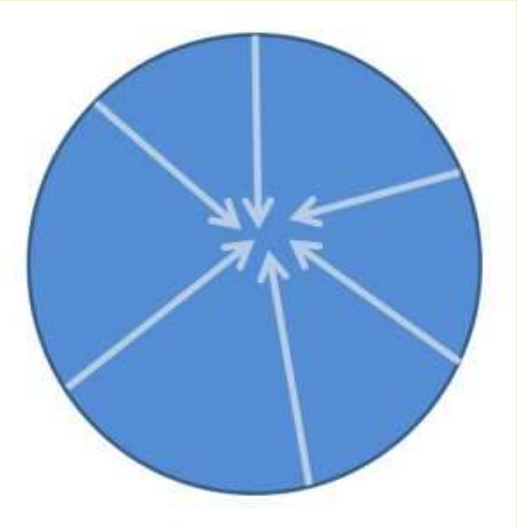
- IC 5: 17,58 %
- Hz: 41,5 %

Calculated vs genomic heterozygousity

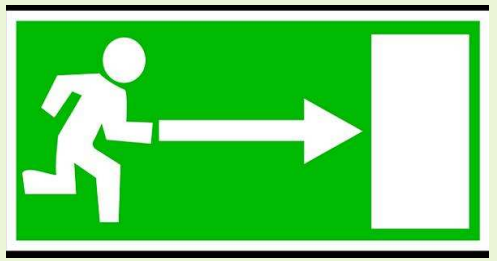


Conclusions

- Do we have a matador problem?
  → yes, very few lines are dominating
- Is the gene pool of the Show Greyhound *really* that small?
  → yes, level of inbreeding is very high, heterozygousity is much lower than the average of all purebred dogs



What to do



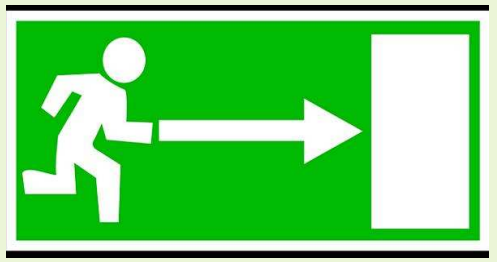
against spinal cysts:

- examine affected dogs (MRI and/or autopsy)
- understand disease mechanisms
- develop a gene test

Maintaining and improving the health status of the Show Greyhound

- Developing new genetic tests every few generations will not change the situation sustainably
- If we really want to improve the health status of the greyhound breed, we have to tackle the root (=the lack of genetic variability), not only the symptom (the disease)

What to do

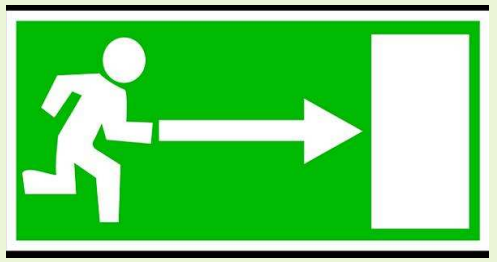


Accept the facts:

- There is NO WAY to „breed away“ from mutations
- There is NO WAY to improve the health status of the population by stronger selection
- There is NO WAY to maintain health with traditional show dog breeding strategies
- „The problem is not that we have a mutation; it's that we don't have a copy of the normal gene" (Carol Beuchat, www.instituteofcaninebiology.org)

Instead: Reduce homozygousity – increase genetic variability

What to do



- **Increase demand!**
- Breed from as many different individuals and bloodlines as possible
- Double matings
- Reduce inbreeding
- Identify breeding matches with higher prospects for heterozygousity by genomic screening
- Outcross to racing/coursing population

→ **Conservation and enlargement of the gene pool**

Genomic screening

- By many breeders, genetic tests are regarded as a threat to the art of breeding and the breeders' individual freedom
- "Geneticists want us to breed for heterozygousity and uneven litters only"
- „Should we plan our matings on the computer now, based on DNA test results only?"
- **NONSENSE! No geneticist would recommend that!**
- DNA screening will NEVER replace a breeder's eye on the dog as a whole! But it should be seen as a valuable additional information
- Smartly used, genomic screening can help to increase genetic variability by maintaining type and soundness…

Thank you for your attention!

Breeders left us a very difficult heritage!

Now it‘s up to us to develop it further – to the worse or to the better…