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Ridge gene test: Its use and potential

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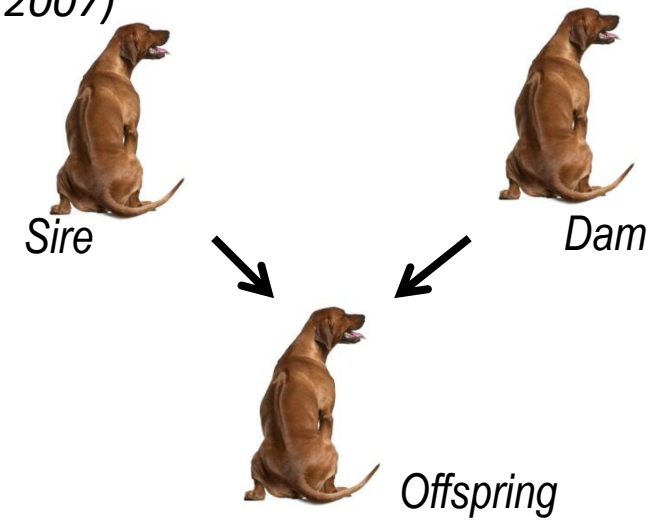
Ridge Genetics

Ridge in Rhodesian Ridgebacks is caused by specific mutation:

~ 133.000 DNA base pairs duplication on canine chromosome 18 = „Ridge gene“

(Salmon Hilbertz, et al.;2007)



Dog might have:

- 2 mutations (duplications; ridge genes) = „R/R“ (*dominant homozygote*)
- 1 mutation (duplication; ridge gene) = „R/r“ (*heterozygote*)
- no mutation (duplication; ridge gene) = „r/r“ (*wild type)*

Ridge Genetics

Ridge formation is caused by presence of single mutation (duplication, ridge gene) = **dominant genetic trait**

Dog might be:

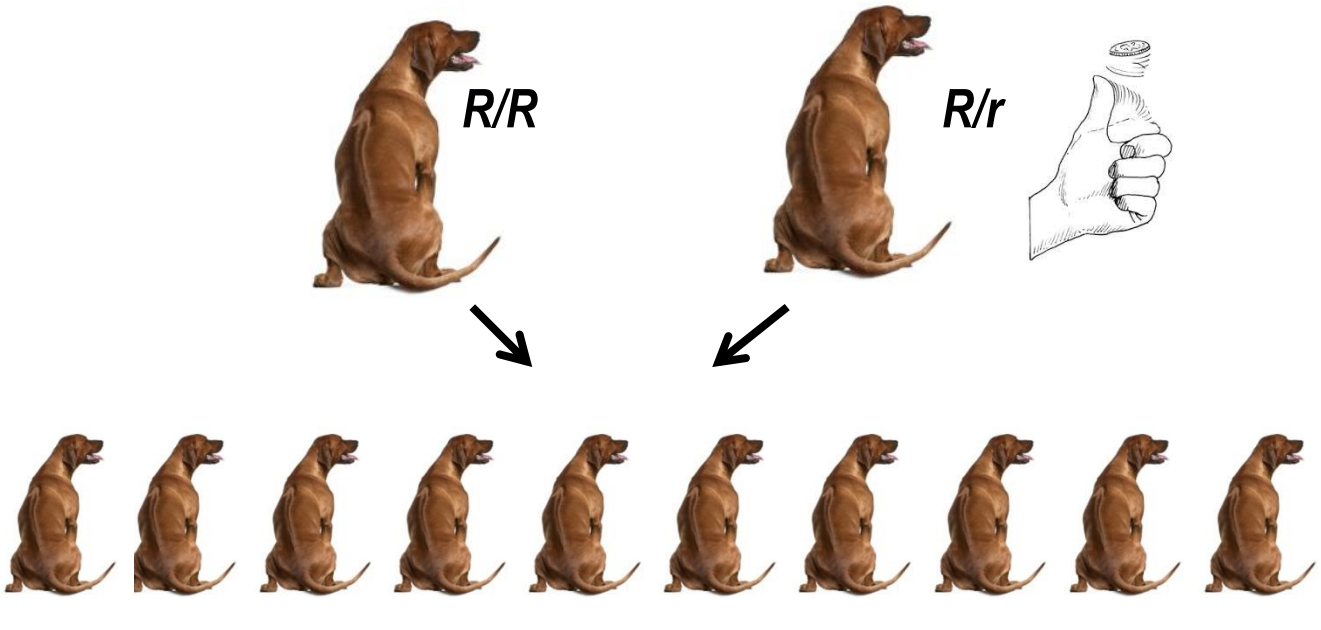
ridged – R/R (=2 mutations, mutation on both chromosomes) –passes ridge gene to all puppies

- R/r (1 mutation on one chromosome, no mutation on another chromosome) – passes mutation only to 50% of puppies – *flip of coin*

ridgeless - r/r (no mutation on both chromosomes) = passes „no mutation“ to all puppies

Ridge Genetics

Mating combination RR x Rr

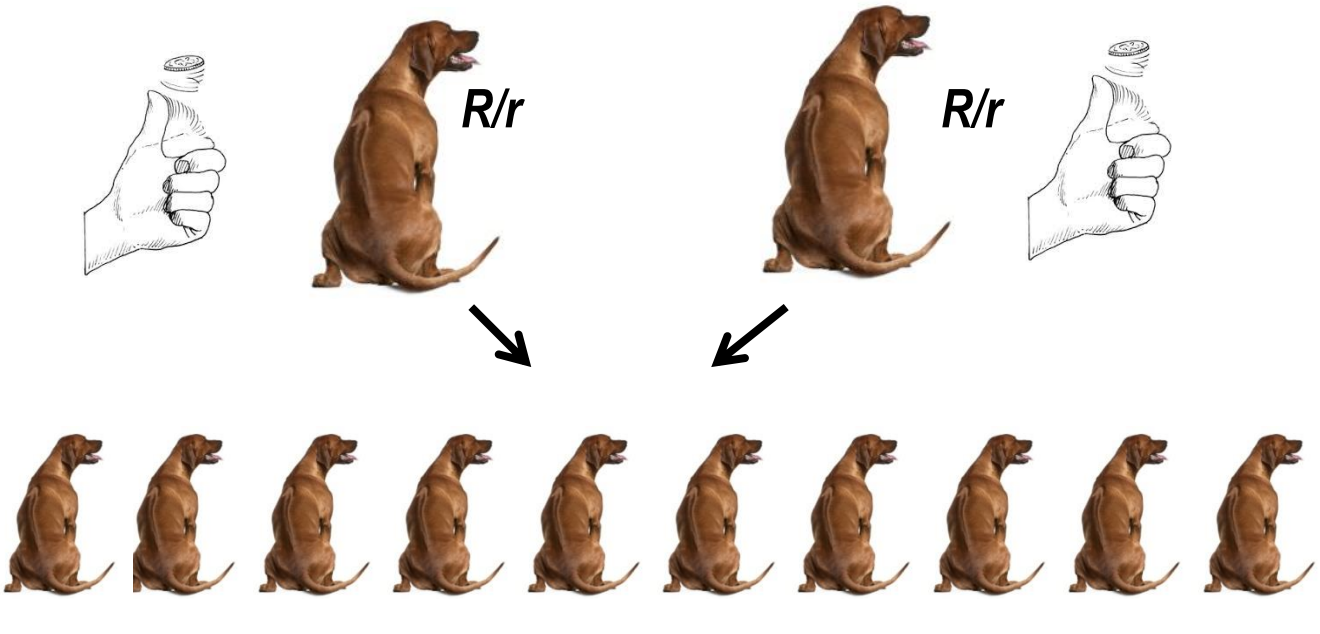


50% R/R + 50% R/r

All puppies expected to be ridged!

Ridge Genetics

Mating combination Rr x Rr



25% R/R + 50% R/r + 25% r/r

25% puppies expected to be ridgeless!

Ridge gene test

Based on physical appearence not possible to distinguish between:
RR – 2 ridge genes and Rr – 1 ridge gene

On several breeders´ requests
- **development of genetic test for ridge disposition** (= copy number of ridge genes)
Veterinary Research Institute, Brno, Czech Republic
from 8/2014

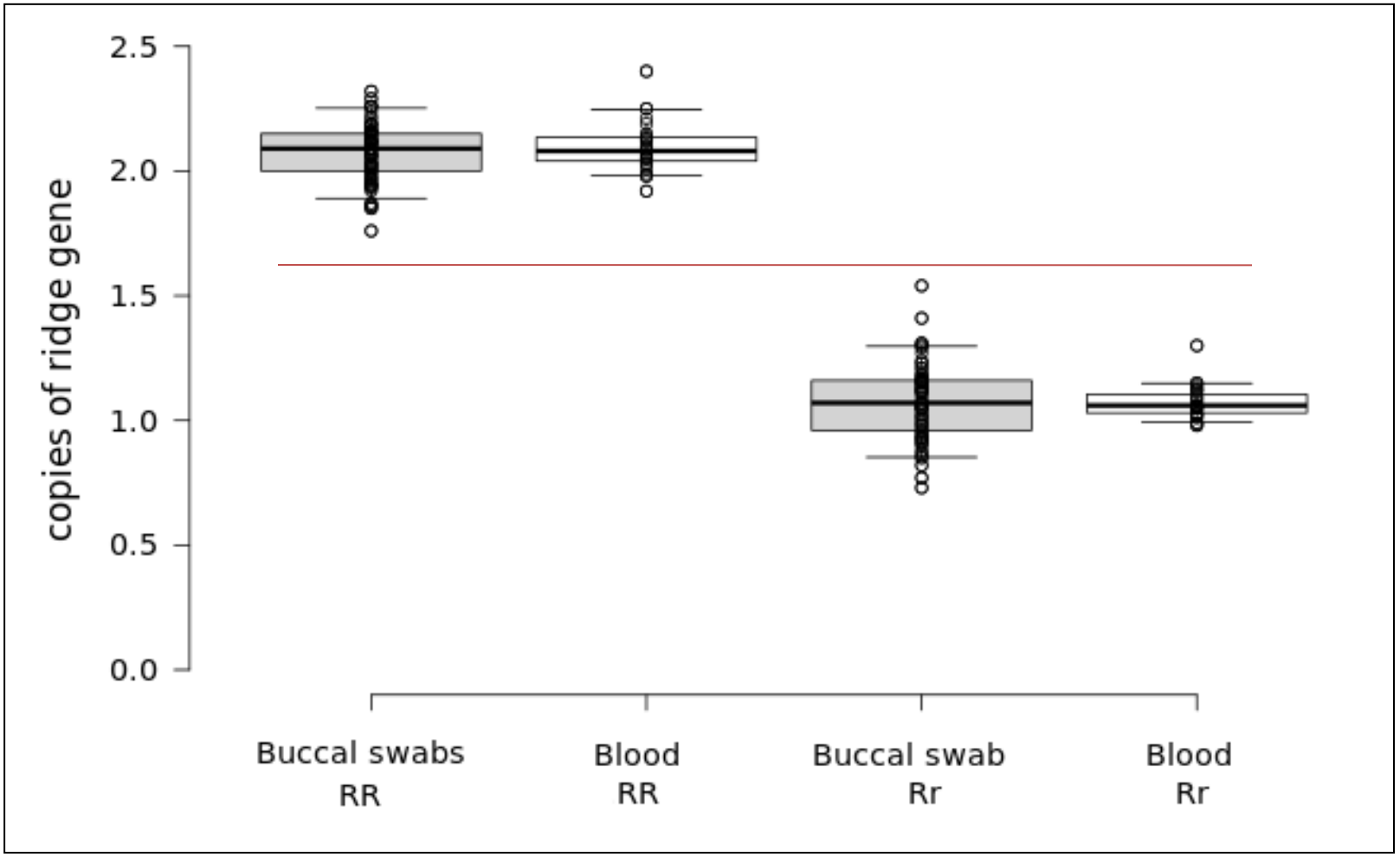
Ridge gene test

- molecular genetic test for copy number of ridge gene = detection of duplications
  result = no ridge gene – rr; 1 ridge gene – Rr; 2 ridge genes – RR

- **Quantitative fluorescent PCR test** based on treshold values

Dog sample:
- blood or buccal swab samples

Ridge gene test

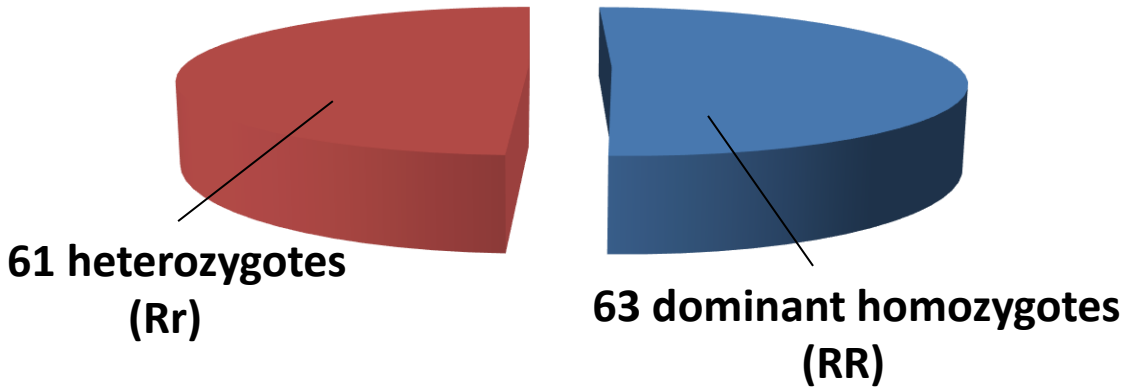


- blood sample: **test accuracy >99%,** (100% analysis success rate)
- buccal swab sample: **test accuracy >96%,** (~80% analysis success rate)

Ridge gene test

- more than 200 samples analysed (commercial + research samples)

124 unrelated dog samples



~75% buccal swabs and 25% blood samples

Ridge gene test – surprising finding

- Some sires or dams with 2 ridge genes (RR) produced ridgeless puppies!

Example 1:

A stud dog (RR) produced 15 litters
- in 14 litters all puppies ridged
- in 1 litter two ridgeless puppies

Stud dog retested –RR confirmed
both ridgeless puppies tested – both Rr

Example 2:

A dam (RR) produced 16 puppies in 1 litter
- 15 pupies ridged, but 1 was ridgeless

Dam retested – RR confirmed
ridgeless puppy tested – Rr!

We genetically confirmed 4 (Rr) ridgeless animals

Ridge gene test – surprising finding

- Dataset analysis (in collaboration with Stephanie Muller – founder of Ridgeback International Database)

RR x Rr mating (confirmed by ridge gene test)
- in total 229 puppies born
- 9 puppies ridgeless

- RR x Rr mating produces ridgeless puppies in 3.9% (9/229)

- RR x RR mating never produced ridgeless puppy

Ridge gene might be silenced (suppresed) occassionally!

Ridge genetics is not governed by simple dominant inheritance, but rather incomplete penetrance model!

Ridge gene test – research samples

- Focus on Dermoid sinus and ridge abnormalities

Dermoid sinus – ridge gene is predisposing genetic factor

Dominant homozygotes (RR) ~5x increased risk for DS

(Salmon Hilbertz, et al.;2007)

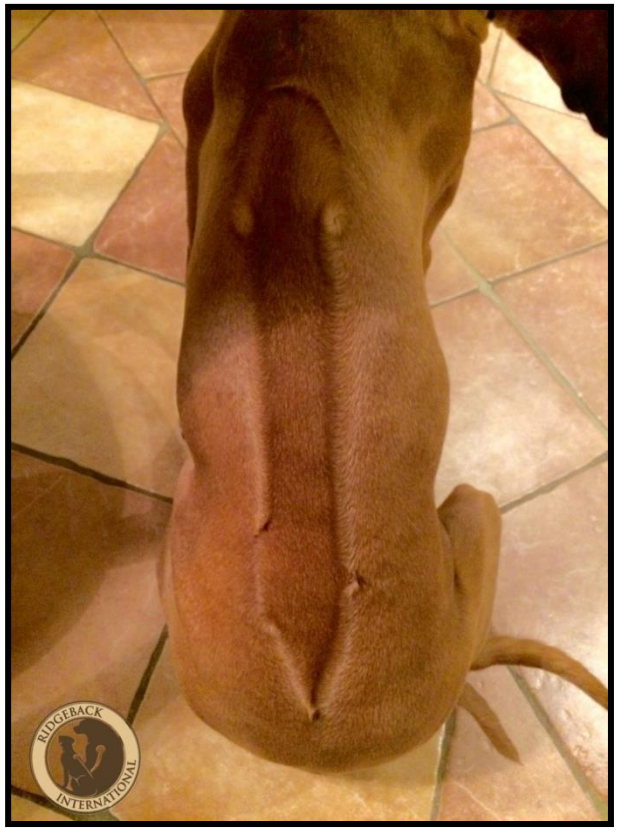
- In our laboratory we confirmed occurrence of DS predominantly in dominant homozygotes (RR)

We request samples of dogs with DS for research

Ridge gene test – research samples

- ridge abnormalities
  - short (partial) ridge
  - mutliple crowns,
  - offset crowns

- We tested several Ridgebacks with multiple crowns – all homozygous (RR)



We request samples of dogs with ridge abnormalities

Summary I

Genetics in Rhodesian ridgeback breeding			
Parents (Sire x Dam)	Puppies		
	ridged	ridgeless	risk of Dermoid sinus
RR x RR	100%	0%	increased
RR x Rr or Rr x RR	>90%	<10%	normal
Rr x Rr	75%	25%	normal / low
RR x rr or rr x RR	>90%	<10%	low
rr x rr	0%	100%	very low

RR – dominant homozygote (2 ridge genes), RR puppy is always ridged
Rr – heterozygote (1 ridge gene), Rr puppy is in 90% ridged, in approx. 10% ridgeless (ridge gene is suppressed)
rr – ridgeless (no ridge gene)

Summary II

- **We developed and validated sensitive ridge gene test for commercial and research use (more info at www. genocan.eu)**

- **The ridge gene (133.4 kb duplication) predispose to ridge formation with incomplete penetrance**
  - ridgeless dogs occasionally carry„silenced“ ridge gene (Rr)
  - approximatelly 8% of heterozygotes (Rr) might be ridgeless (deduced from RR x Rr mating)

- **Dominant homozygotes (RR) are predisposed to DS occurence and very likely to some ridge abnormalities (multiple crowns)**

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Acknowledgements:

Duplication of *FGF3*, *FGF4*, *FGF19* and *ORAOV1* causes hair ridge and predisposition to dermoid sinus in Ridgeback dogs

Nicolette H C Salmon Hillbertz[1], Magnus Isaksson[2], Elinor K Karlsson[3,4], Eva Hellmén[2,5], Gerli Rosengren Pielberg[6], Peter Savolainen[7], Claire M Wade[3,8], Henrik von Euler[9], Ulla Gustafson[1], Åke Hedhammar[9], Mats Nilsson[2], Kerstin Lindblad-Toh[3,6], Leif Andersson[1,6] & Göran Andersson[1]

The dorsal hair ridge in Rhodesian and Thai Ridgeback dogs is caused by a dominant mutation that also predisposes to the congenital developmental disorder dermoid sinus. Here we show that the causative mutation is a 133-kb duplication involving three fibroblast growth factor (FGF) genes. FGFs play a crucial role in development, suggesting that the ridge and dermoid sinus are caused by dysregulation of one or more of the three FGF genes during development.

the ridged Hottentot Khoi dog[1]. The Thai Ridgeback (**Fig. 1b**) and the Vietnamese Phu Quoc dog are two Asian breeds with a dorsal hair ridge closely resembling the one found in Rhodesian Ridgeback dogs.

Histology of the skin from a ridged dog, taken strictly from the dorsal median plane, showed cross-sectioned appendages (that is, hair follicles and sebaceous glands) of normal appearance but lateral orientation (**Fig. 1d**). In contrast, skin from the median plane of a ridgeless dog showed caudally oriented hair follicles (**Fig. 1e**). Ridgeback dogs are affected by the congenital malformation dermoid sinus

http://www.nature.com/naturegenetics Publishing Group

- Nicolette Salmon Hillbertz *et al*.,
  Upsala University, Sweden

- Czech Rhodesian Ridgebacks Breeding Club (KCHRR)
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- Ridgeback International (Stephanie Muller)