TIBETAN TERRIER World Congress 24 & 25 September



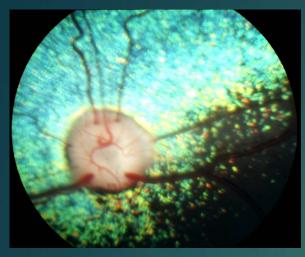
9h30 / 10h	Dr Gilles Chaudieu - Ophtalmologist - Dip ECVO Eye diseases : hereditary or not ?
10h / 10h30	Pr Jean Pierre Genevois - Orthopedist - Expert of the FCI scientific commission Normal hips : what are the criteria? .
10h30/ 10 h 45	Break
10 h 45 / 11 h 15	Fleur Marie Missant – SCC Health and Genetic Resources Project Manager: Genomics as an aid to diagnosis
11 h 15 / 11 h 45	Dr Daniel Combarros – Dermatologist – Professor at the Veterinary school lof Toulouse Itching: understanding it, treating it, prevent it
11h45 / 12 h 30	Round table - Discussion

14 h / 14 h 40 14 h 40 / 15h 10	Mark James / Glenn Davies : Tibetan terriers. A passion, knowledge and understanding. Dr Mike Tempest (Mikudi TTs, UK) : An analysis of the 2019 genetics paper and what it means for the breed
15h10 / 15h30	Break
15h30 / 16h30	Round table; standards and question about the breed : Brian Harris – Mike Tempest – Mark James - Sabine Schiratti - Lydie Estru – Gauthier Lequain



Dr Gilles Chaudieu Ophtalmologist - Dip ECVO

Eye diseases hereditary or not?



Eye diseases: hereditary or not?

Les maladies oculaires: héréditaires ou non?

G. Chaudieu, DV, Dip ECVO, DESV OV 63122 F-Ceyrat

TIBETAN TERRIER WOLD CONGRESS, 24-25 SEPT.2022

Two questions as an introduction... Deux questions en introduction...

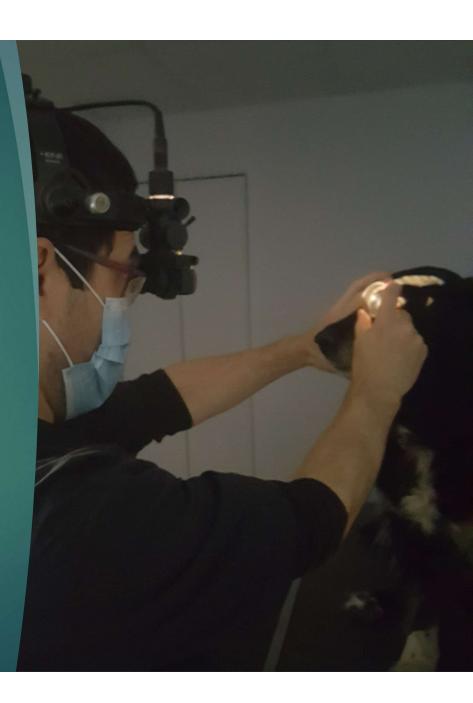
Related dogs are they always available for eye examination?

Les sujets apparentés sont-ils toujours à disposition pour les examens oculaires?

Is the additional economic burden of a systematic examination for inherited ocular diseases acceptable?

Le surcoût représenté par l'examen systématique de dépistage des maladies oculaires héréditaires est-il une contrainte acceptable?

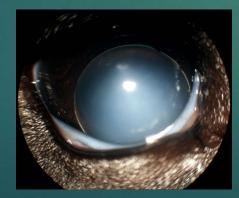
If the answer is yes twice, this lecture could be justified Si la réponse est deux fois oui, cette présentation est justifiée!



When do we suspect that an ocular disease is inherited?

Quand suspecter qu'une maladie oculaire est héréditaire?

- 1. Frequency greater than in other breeds
 Fréquence supérieure à celle observée dans les autres races
- Frequency increasing in the breed
 Fréquence en augmentation dans la race
- 3. Frequency greater in related dogs in the breed Fréquence plus élevée chez les apparentés au sein de la race
- 4. Age of onset and course of progression predictible Âge d'apparition et évolution prévisibles



Primary lens luxation

- 1, 2. 20 cases of lens luxation in Britishbred Tibetan terriers, together with a further seven from Sweden.
- 3. High levels of inbreeding ranging from 0 to 24,3 per cent, with a mean of 14,3 per cent; all affected cases traced back to one or more of three animals on both sides of their pedigrees, all three being breed champions.
- 4. The age at onset is three to five years, the PLL may result in elevation of IOP causing vision impairement or blindness.

Willis MB, Curtis R, Barnett KC, Tempest WM. Genetic aspects of lens luxation in the Tibetan terrier. Vet Rec. 1979; 104: 409-12.

When do we suspect that an ocular disease is inherited?

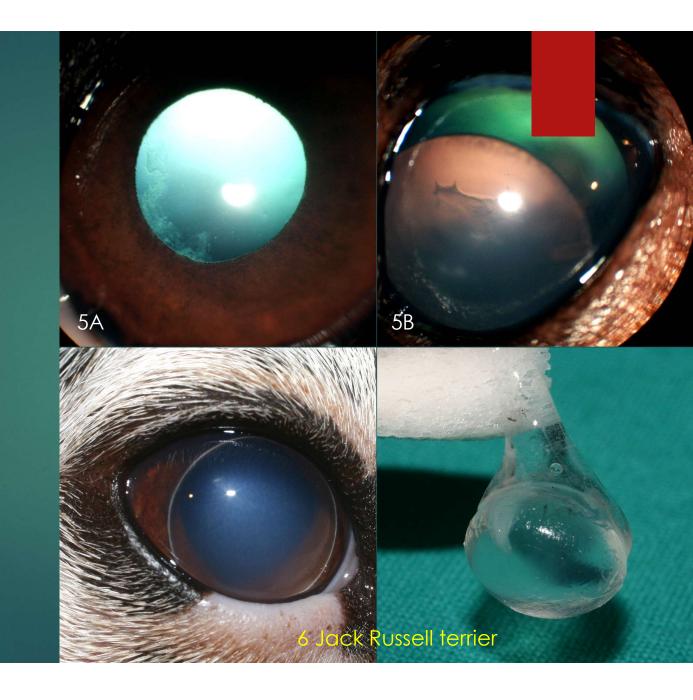
Quand suspecter qu'une maladie oculaire est héréditaire?

5. Characteristic clinical signs

Signes cliniques caractéristiques

▶ 6. Identical to a disease proven to be inherited in an other breeed

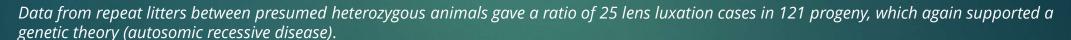
Signes identiques à ceux observés dans une race où l'origine héréditaire est avérée



Critères requis pour reconnaître une maladie oculaire comme héréditaire ou présumée héréditaire

1. Published reports in the literature with evidence of inheritance, or presumed inheritance in the breed

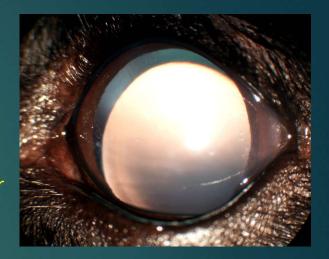
Publications scientifiques rapportant la maladie comme héréditaire ou présumée héréditaire

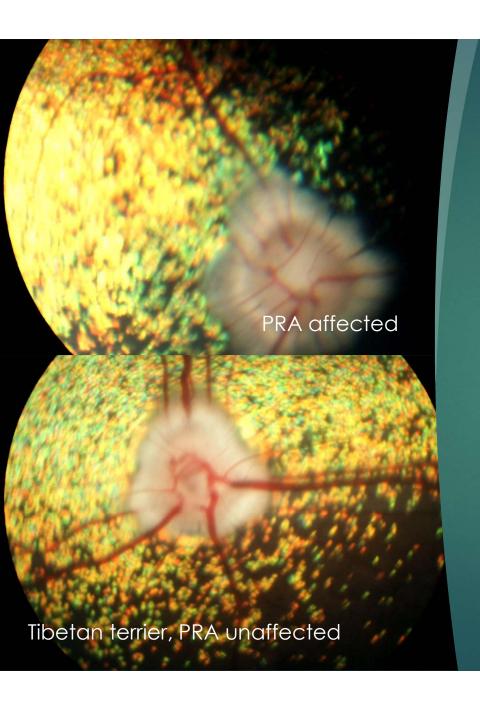


Willis MB, Curtis R, Barnett KC, Tempest WM. Genetic aspects of lens luxation in the Tibetan terrier. Vet Rec. 1979; 104: 409-12.

Primary lens luxation (PLL) is a well-recognized, painful and potentially blinding inherited ocular condition in dogs. PLL-affected dogs of 30 different breeds were screened, to identify those which carried a previously described c.1473+1 G>A mutation in ADAMTS17 that is associated with PLL in Miniature Bull terriers, Lancashire Heelers, Tibetan terriers and Jack Russell terriers.

Gould D, Pettitt L, Mc Loughlin B, Homes N, Forman O, Thomas A et al. ADAMTS17 mutation associated with primary lens luxation is widespread among breeds. Vet Ophthalmol. 2011;14:378-84.





Critères requis pour reconnaître une maladie oculaire comme héréditaire ou présumée héréditaire

2. Clinical confirmation of affected dogs in a breed (reference: CERF, ACVO genetic guidelines in making breeding recommendations)

Confirmation clinique de chiens atteints dans la race (référence: CERF, ACVO genetic guidelines)

- Incidence of affected individuals > 1% of the examined population with a minimum of 5 dogs affected/5 year period
- Regardless of the population examined, if at least 50 affected dogs are identified in a 5 year period, the concerned disease is listed for the concerned breed

Important: the sensitivity of detection is greater when a large number of dogs is examined!

PRA « all forms », in: Ocular disorders report, ACVO: 1991-2014: 8017 Tibetan terriers examined, 121 PRA (1,5%) 2015-2019: 1274 Tibetan terriers examined, 3 affected (0,2%)

Critères requis pour reconnaître une maladie oculaire comme héréditaire ou présumée héréditaire

➤ 3. A request from the breed club to the Scientific Committee of the SCC (french kennel club) that the disease may be included for the breed, submitted to:

Demande du Club de race adressée à la commission scientifique de la SCC pour inclure la maladie dans celles recherchées dans la race, soumise à:

- Documentation relative to the disease, number of cases reported in the breed
- Critical examination of the Scientific Committee and possible classification of the disease under a level of priorities:
 - « emerging » diseases

annual reevaluations

- included diseases
- ▶ Agreement of the Scientific Committee

Persistent pupillary membrane (PPM)

- Minor forms only (iris-iris, pigment foci): 9,9% (CERF/ACVO), 6,8% (personal)
- Iris-cornea, iris-lens, sheets: <0,5% (CERF/ACVO, 1274 dogs examined), 0 (personal)
- Suspected inherited?



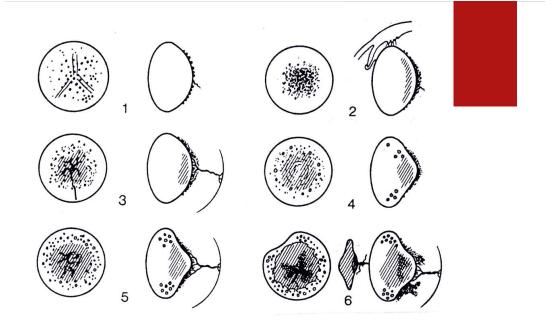
Critères de requis pour reconnaître une maladie oculaire comme héréditaire ou présumée héréditaire

4. Clinical experience of one or several national Eye Scheme Panelists indicating a particular condition in the breed without scientific publication or previous evidence of affected dogs

Expérience clinique d'un ou plusieurs Examinateurs nationaux rapportant une situation compatible avec la présence d'une maladie oculaire présumée héréditaire pas encore signalée dans la littérature ou antérieurement dans la race

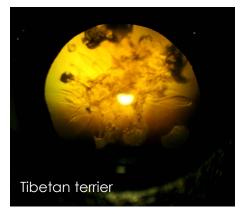
Persistent Hyperplastic Tunica Vasculosa lentis/Persistent Hyperplastic Primary Vitreous (PHTVL/PHPV) in the Tibetan Terrier:

- some cases observed (grade 2-6 under Stades classification, that means visual impairment)
- reported in other breeds (Doberman Pinscher, Staffordshire Bull Terrier...) as autosomal dominant with a strong penetrance)
 - suspected inherited in the Tibetan Terrier?

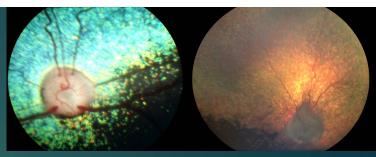


PHTVL/PHPV (from Stades FC. Persistent hyperplastic tunica vasculosa lentis and persistent hyperplastic primary vitreous (PHTVL/PHPV) in 90 closely related Doberman Pinschers: clinical aspects. J Am Anim Hosp Assoc. 1980; 16:739-51)





Critères requis pour reconnaître une maladie oculaire comme héréditaire ou présumée héréditaire



PRA 3

PON, 8 yo (court B. Michaud)

▶ 5. Results of genetic reseach and genetic testing in a significantly representative population of the breed

Études génétiques fondamentales et validations populationnelles significatives dans l'effectif racial

Clinical follow up essential!

PRA3, late onset disease (clinical signs when 4-5 yo): PRA in the TS has not previously been associated with any genetic variants. Using a GWA mapping approach, a novel candidate variant, FAM161A, was identified that is likely to represent a major causal mutation for PRA in the TS. While this mutation does not account for all cases of PRA in this study, suggesting that there are additional loci causing PRA in this breed, it does appear to be highly penetrant and a major cause of PRA in this breed. While PRA3 is also present in TT, as they are closely related and the mutation has not been found in any other breeds, the mutation appears to be confined to these two breeds.

Downs LM, Mellersh CS (2014). An Intronic SINE Insertion in FAM161A that Causes Exon-Skipping Is Associated with Progressive Retinal Atrophy in Tibetan Spaniels and Tibetan Terriers. PLoS ONE 9(4): e93990. doi:10.1371/journal.pone.0093990

PRA4, late onset disease, slowly progressive: This is the same mutation previously found to cause PRA in Gordon Setters and Irish Setters, and it was later found in Tibetan Terrier, Standard Poodle and the Polski Owczarek Nizinny. The presence of the mutation in such a diverse range of breeds indicates an origin preceding creation of modern dog breeds. Hence, we screened 262 dogs from 44 different breeds plus four crossbred dogs, and can subsequently add Miniature Poodle and another polish sheepdog, the Polski Owczarek Podhalanski, to the list of affected breeds.

Karskov-Mortensen P, Proschowsky HF, Gao F, Fredholm M. Identification of the mutation causing progressive retinal atrophy in Old Danish Pointing Dog. 2018. Anim Genet; 49: 237-41.

PRA of PON dogs and Tibetan terriers is a late-onset degenerative disease with slow progression. There is early loss of rod function, while the cone system deteriorates later. Svensson M, Olsén L, Winkler PA, Petersen-Jones S. Progressive retinal atrophy in the Polski Owczarek Nizinny dog: A clinical and genetic study. Vet Ophthalmol. 2015; 19: 195-205

Conclusion

- ▶ Diagnosis under a reliable scheme is the rule before considering an ocular disease as inherited
- Genetic test is a useful/powerful complementary procedure when existing
- ► A large clinical follow-up is the condition to evaluate the situation in a breed

Thank you for attention!



Professeur Jean-Pierre Genevois Orthopedist - Expert of the FCI scientific commission

Normal hips what are the criteria?

Tibetan terriers world congress
Agnetz, september 25th
2022

Normal hips



what criteria?



Pr. Jean-Pierre GENEVOIS

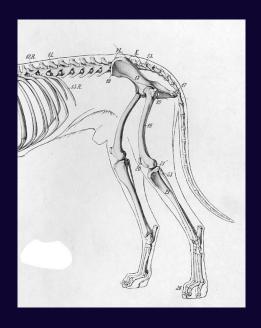
Hip joint = submitted to huge mechanical strains

role ++ standing & sitting position, transmission of impulses from hind leg to the body

very big range of motion (extension/flexion, abduction/adduction external rotation / internal rotation),

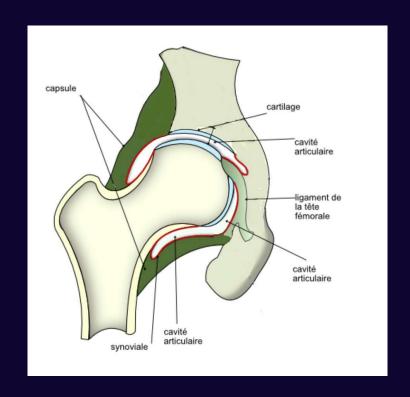








normal hip :
femoral head deeply seated
(« covered »)
in the acetabulum



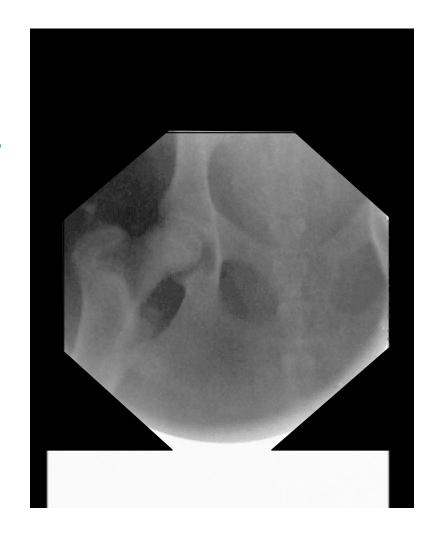
Hip joint = synovial joint



normal hip=stable (tight) hip
! the femoral head remains deeply seated
in the acteabular cavity during all the movements
! no lateral movements allowed
outside of the acetabulum

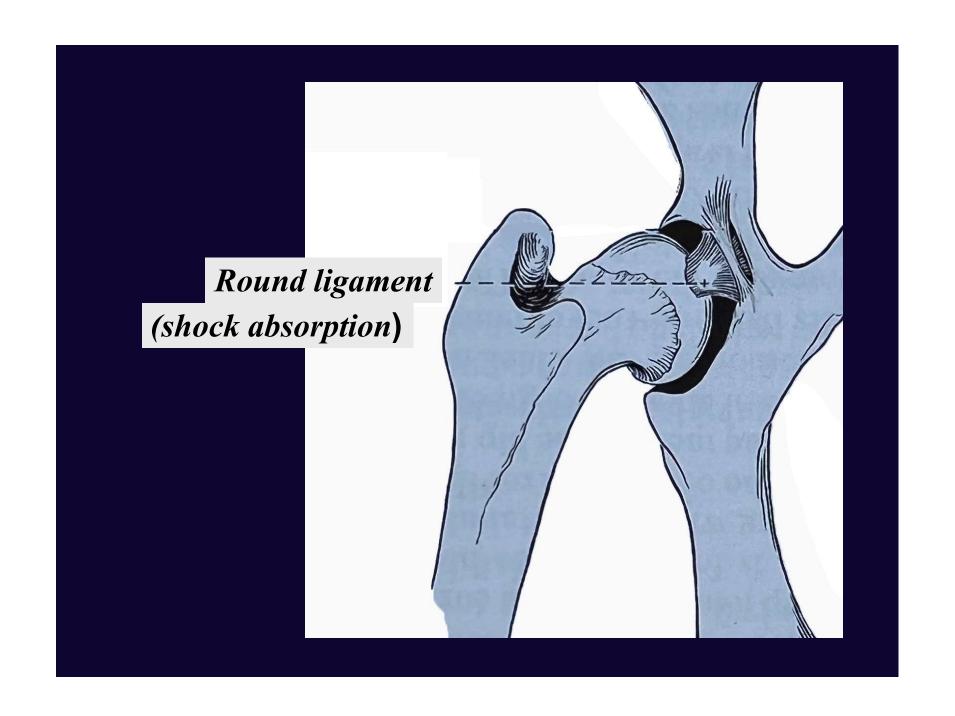
Stable (tight) hip

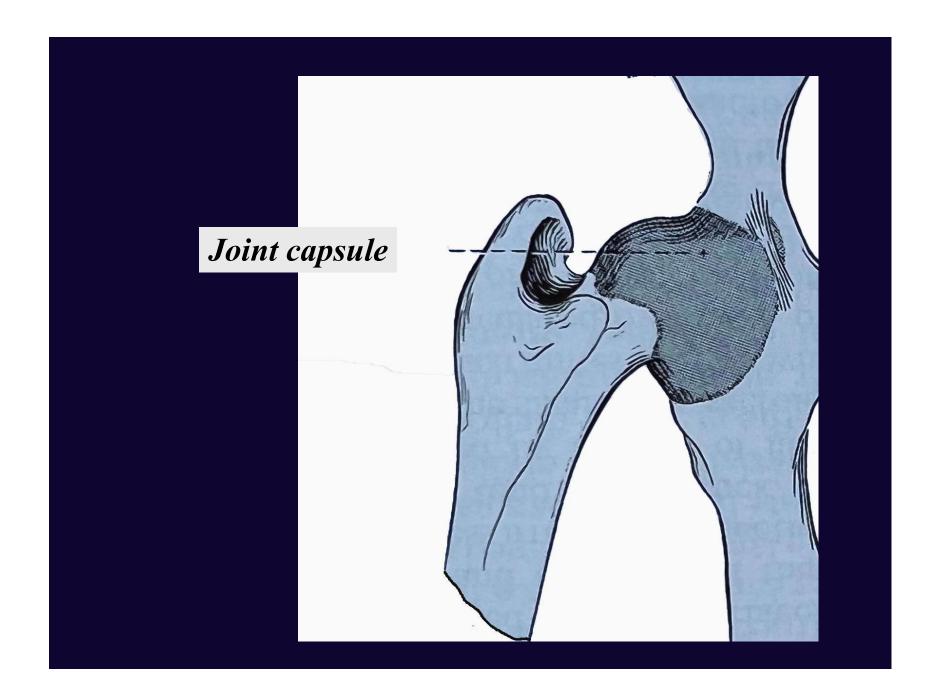
stays perfectly seated in the acetabular cavity



Crédit: Aldo VEZZONI

on what relies
the hip joint stability
?

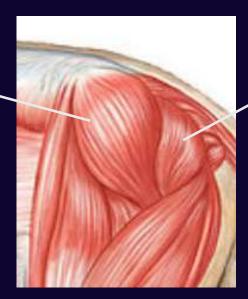




active stability gluteus muscles



Gluteus medius



Gluteus superficialis

+ deep gluteus (hidden)

Forces exerted on the hip joint depending on biomechanical

conditions Conditions biomécaniques	Forces de réaction articulaire
Appui sur 4 membres	0,07 PV
Appui sur 3 membres	0,7 PV (x10)
Marche (2 m/sec)	1,4 PV (x20)
Course (15 m/sec)	4,6 PV (x65)

illustration of the FH pressure surface on the acetabulum normal hip : dorsal « coverage » = at least 50% of FH



Repris de Biomécanique de la hanche du chien - A. AUTEFAGE CES Orthopédie – ENVT- 2022

HIP DYSPLASIA =

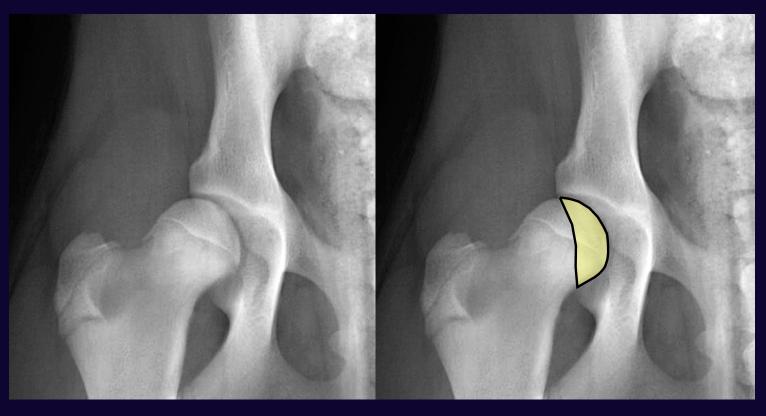
developmental condition linked to joint instability

resulting at +/- long term in joint profile alterations and osteoarthritic development



instability: the femoral head can «move out» of the acetabulum

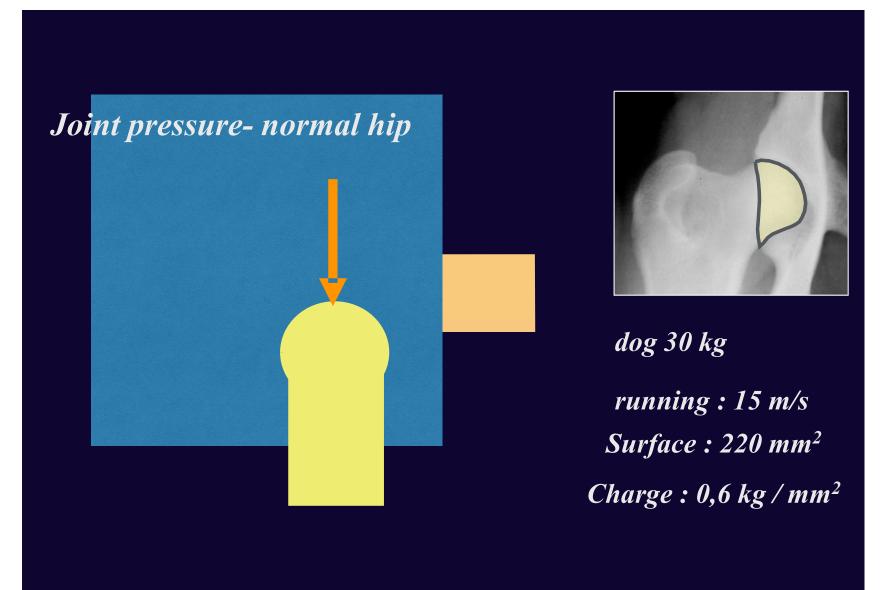
instabilit (sub-luxation) illustration of the pressure surface (moderate hip dysplasia)



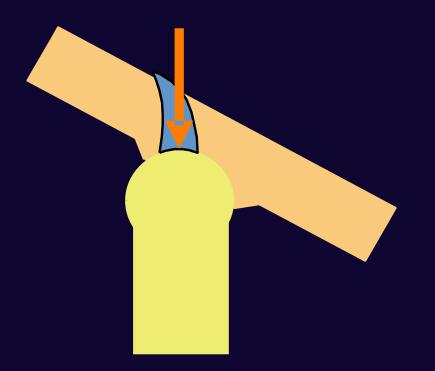
Repris de Biomécanique de la hanche du chien - A. AUTEFAGE CES Orthopédie – ENVT- 2022

consequences of femoral head position on the pressure zone





Joint pressure- moderate hip dysplasia



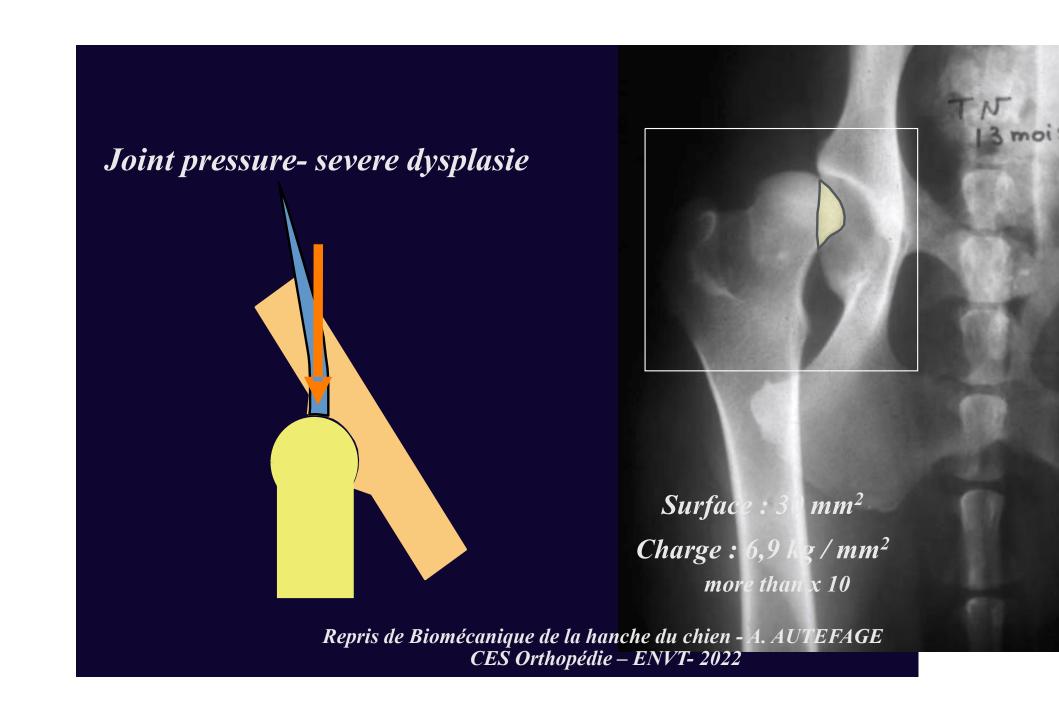


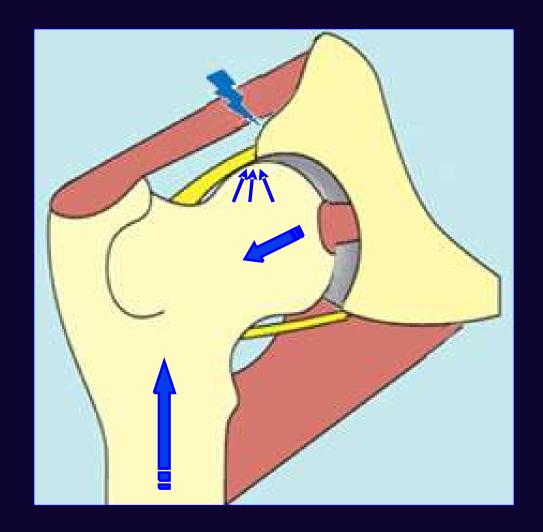
dog 30 kg

running: 15 m/s

Surface: 110 mm²

Charge: 2,0 kg/mm²
more than x 3



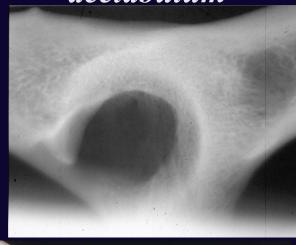


bad pressure distribution

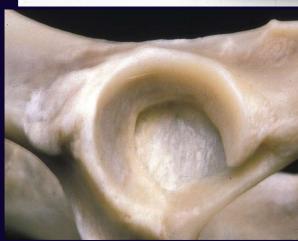
cartilage lesions
underlying bone lesions
(shallow
jacetabulum)
joint inflammation

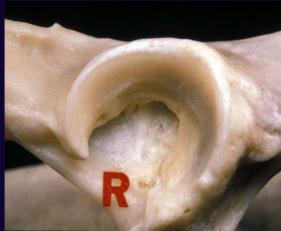
Modifié d'après DEROY-BORDENAVE et coll, Le Point Vétérinaire, Mai 2016, 365, 20-42 normal acetabulum











Repris de Biomécanique de la hanche du chien - A. AUTEFAGE CES Orthopédie – ENVT- 2022

BARDENS



ORTOLANI test





Perfect Hip Even joint space rounded cranial acetabular rim excellent dorsal femoral head coverage

lateral narrowing of joint space
craniolateral rim diverges
poor dorsal femaral head coverage

Imperfect hip







HD official radiographic screening standard position (growth end)

TT, sometines difficult to achieve

very abundant coat difficult to check anatomical landmarks

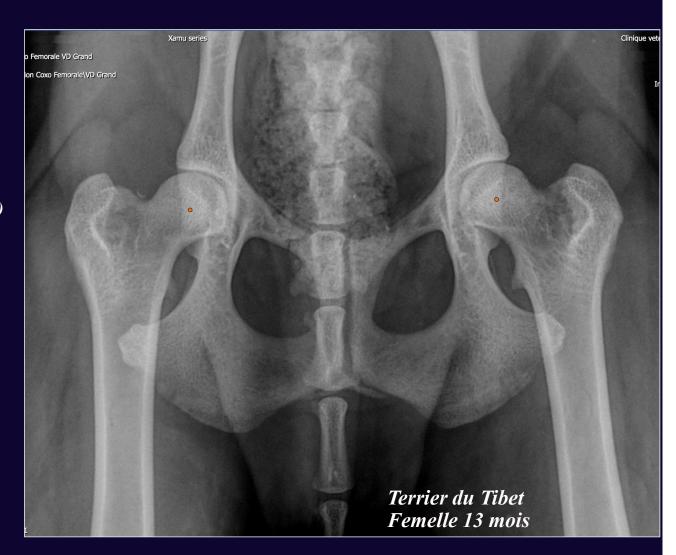
Not very « padded » rear end

Pb of pelvic symmetry
Pb of patellar positioning

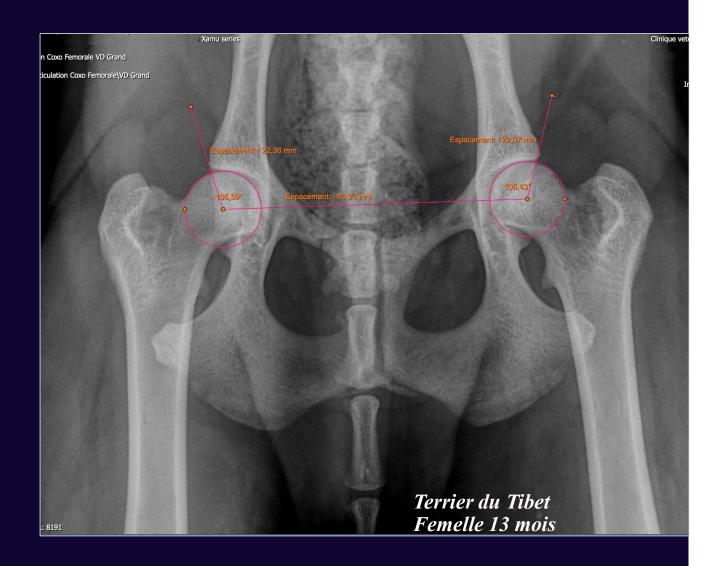




position FH center (dorsal coverage quality)



Crédit Dr G. CHAUDIEU



Norberg Angle

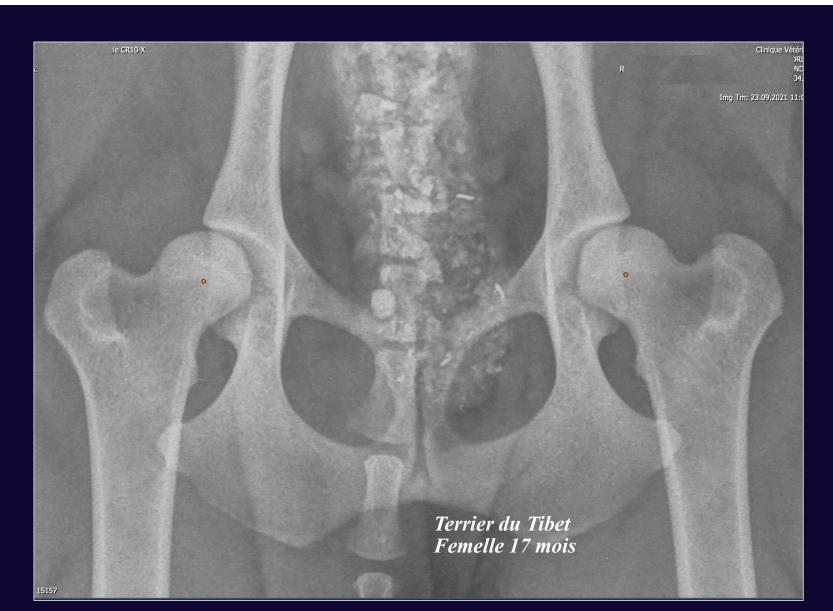




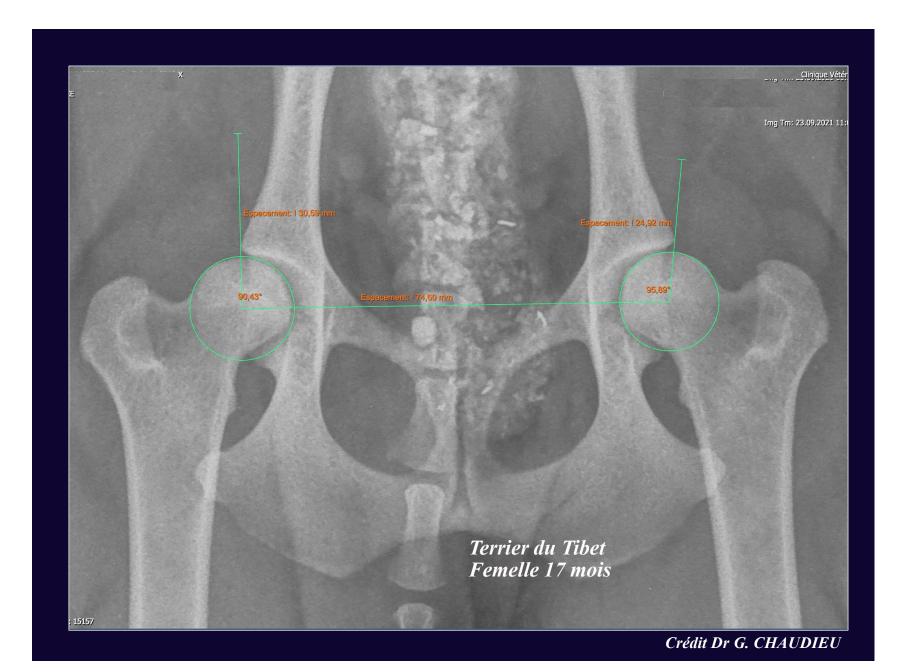
Terrier du Tibet Femelle 13 mois



Terrier du Tibet Femelle 17 mois



Crédit Dr G. CHAUDIEU











acetabular osteophytes

• Osteoathritic modifications





FCI classification

(Europe, except UK)

5 grades

A: no sign of HD

B: near normal

C: mild HD

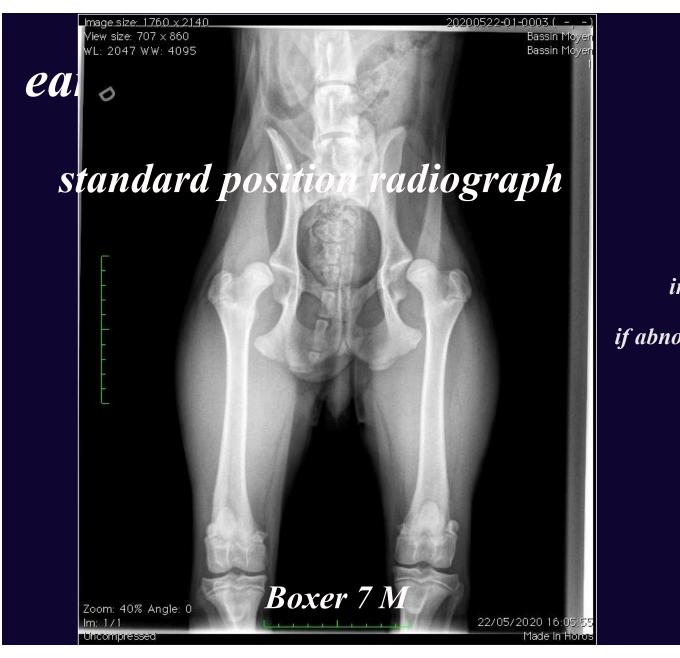
D: moderate HD

E: severe HD

early dic



Newfounland 4 M

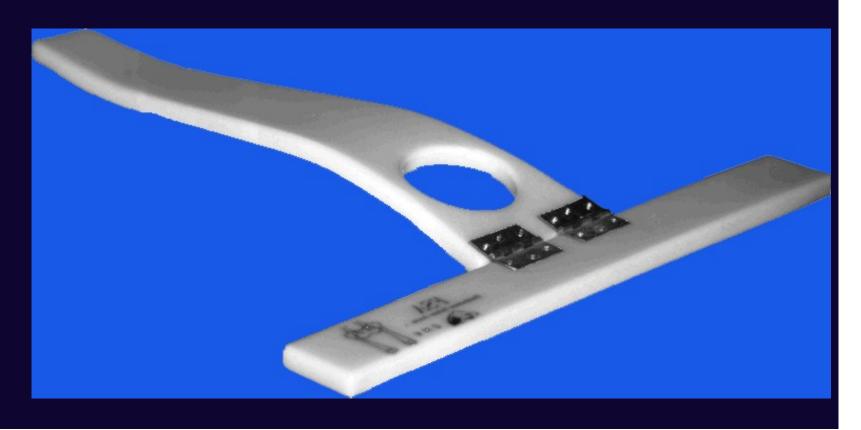


informative only if abnormality detected

Early measurement of hip joint laxity (stress radiographic methods)

PennHip - SMITH G.K. & coll JAVMA 1990,196, 1, 59-70

A.VEZZONI distractor



Early measurement of hip joint laxity (stress radiographic methods)



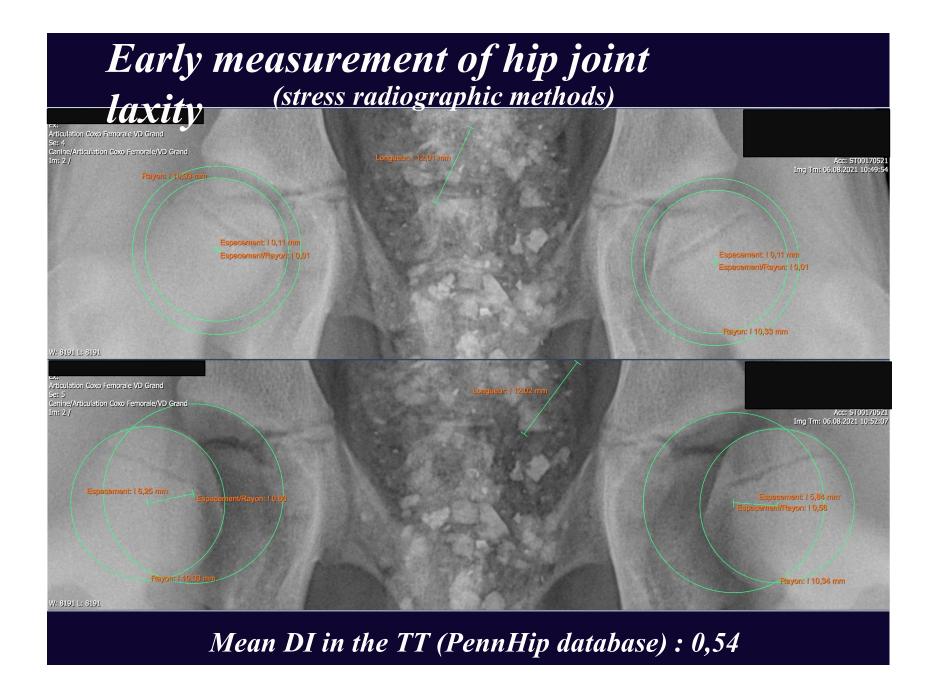


compression view



Early measurement of hip joint laxity (stress radiographic methods)





breed « anatomical linkesptosstjøtjon: shallow acetabulum



Bouledogue anglais Femelle 11 mois

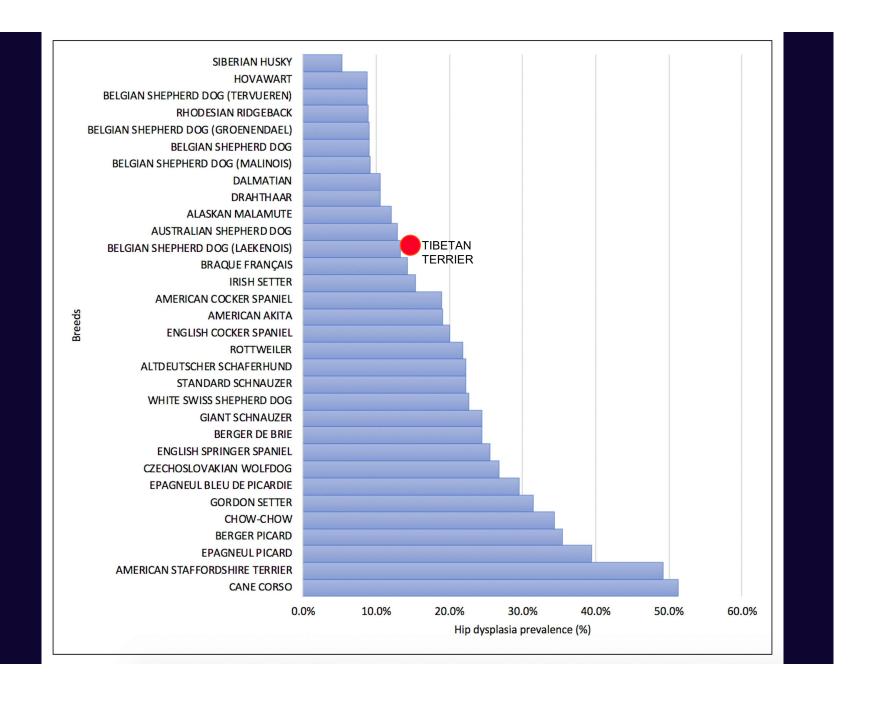


Sussex Spaniel Femelle 12 mois



paradoxically not always lameness (quality of gluteus muscles)

starting conditions (HD prevalence) variable among breeds



starting conditions (HD prevalence) variable among breeds

the role of official radiographic scrutineer(s) in conjonction with people in charge of breed-club

is important to favour as breeding dogs good hip individuals

depending on the starting point in the breed the aim is to progressively improve the condition

mass phenotypic selection is efficient on long term

BALDINGER A., GENEVOIS JP. & Coll, Prevalence of canine hip dysplasia in 10 breeds in France, a retrospective study of the 1997-2017 radiographic screening period, PLOS ONE (2020), July 9, 1-11, https://doi.org/10.1371/journal.pone.0235847

GENEVOIS JP., BALDINGER A. & Coll, Prevalence of canine hip dysplasia in 17 breeds in France, a retrospective study of the 1993—2019 radiographic screening period Revue vétérinaire clinique (2020) 55, 123—146 https://doi.org/10.1016/j.anicom.2020.09.003

progress is slow, selection policy need to be carried out with perseverance

«5 generation» pedigrees
publication of « negatives informations » on the pedigree
(if transmitted by breed club)

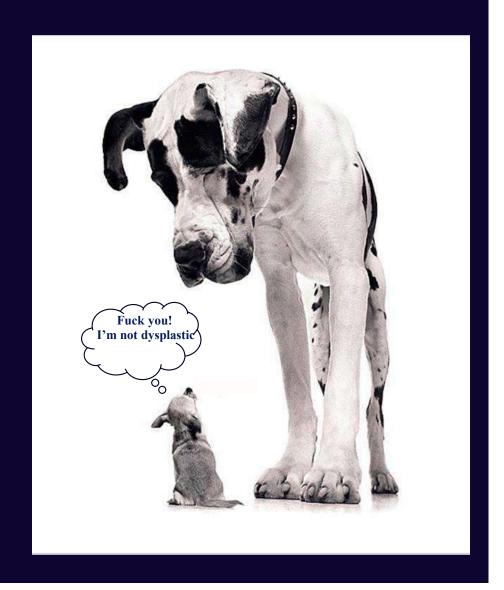
calculation and use of EBV (estimated breeding value)

(= « positive effect » individual s & « negative effect » individuals)

LOF SELECT

look for a specific dog results look for progenitors create a virtual mating

Thank you for your attention





Fleur Marie Missant

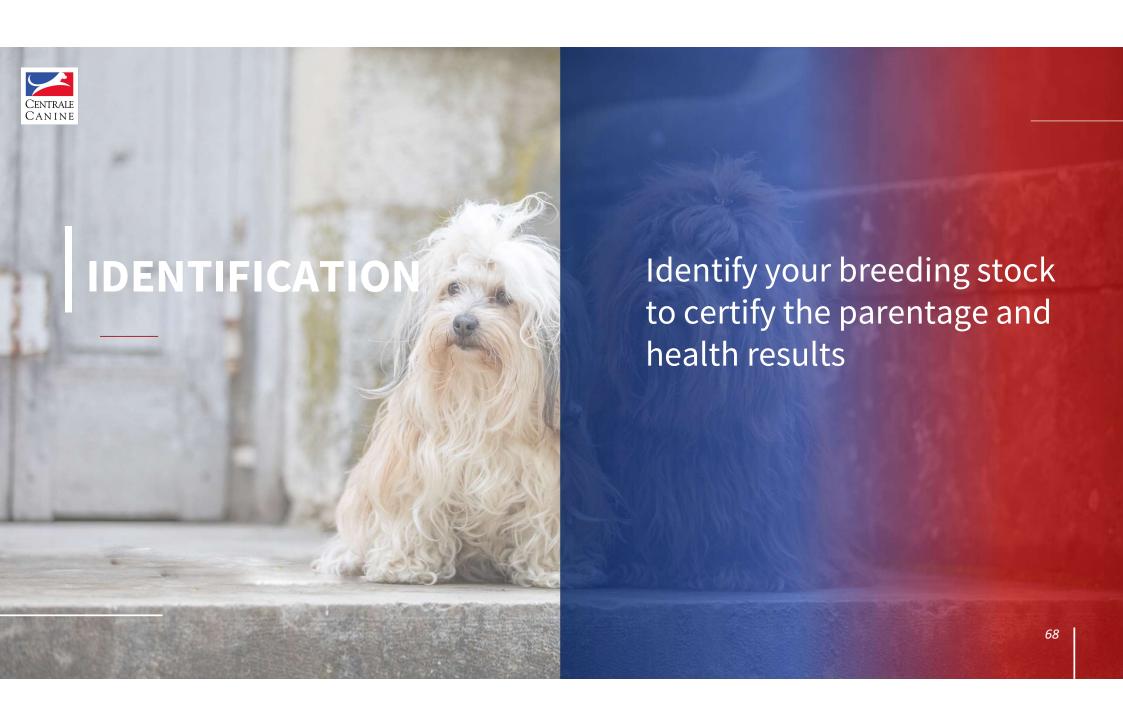
SCC Health and Genetic Resources Project Manager

Genomics as an aid to diagnosis



GENOMICS AS AN AID TO DIAGNOSIS

Tibetan Terrier Congress 2022

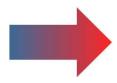






Panel of 22 STR markers

International norm ISAG 2006



Unique identification for each dog

Certificat d'Identification Génétique

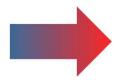
Marqueur	Allèle 1	Alléle 2	Marqueur	Alièle 1	Aliéle 2
AHT121	98	102	INRA21	101	105
AHT137	141	141	INU005	124	128
AHT130	119	121	INU030	146	152
AHTh171	219	219	INU055	218	220
AHTh260	246	246	REN105L03	233	233
AHTk211	89	89	REN162C04	202	206
AHTk253	292	296	REN169D001	218	218
AMELOGENIN	Y	Х	REN169018	158	170
CXX(279	124	126	REN274M23	268	272
FH2054	148	156	REN54P11	222	232
FH2848	236	240	REN64E19	145	147

NEW GENETIC IDENTIFICATION



ISAG 2020: a new panel of markers with a new technology = genomics

Panel of 22 STR markers



2 panels of 100 SNP markers

Already used all around the world Easy to find in a lot of labs

More precise results
The technology of tomorrow





How does it work?

Comparison between the DNA prints of the 2 parents and the offspring

Certificat d'Identification Génétique

Marqueur	Allèlei	Allele 2	Marqueur	Allèle 1	Allele 2
AHT121	98	102	INRA21	101	105
AHT137	141	141	INU006	124	128
AHT130	119	121	INUoso	148	152
AHTh171	219	219	INU055	218	220
AHTh260	246	246	REN105L03	233	233
AHTk211	89	89	REN162C04	202	206
AHTk253	292	298	REN169D001	218	218
AMELOGENIN	Y	X	REN169018	158	170
CXX(279	124	128	REN274M28	268	272
FH2064	148	158	REN54P11	222	232
FH2848	236	240	REN64E19	145	147





How does it work?

Comparison between the DNA prints of the 2 parents and the offspring

STR: If more than 1 marker does not fit → parentage is not validated

SNP: If more than 4 markers do not fit \rightarrow parentage is not validated



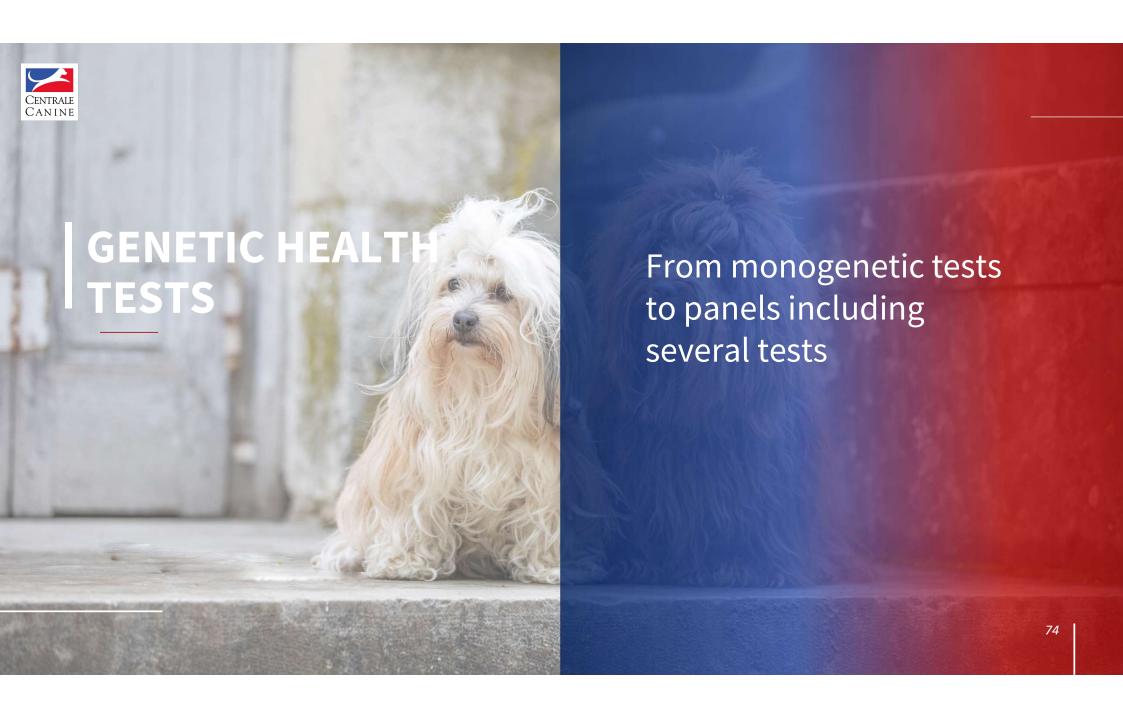
You cannot compare DNA prints in the different methods

PARENTAGE COMPATIBILITY



Benefits

- Certification of the Studbook
- Selling litters with certified origins
- Genetic health test results are transmitted by heredity
- Litters with two fathers are authorized



PANELS



A good opportunity for selection

- ➤ 1 analysis for more than 200 results
- Genetic identification
- Monogenetic results : health tests and traits
- > SNP markers panel to study genetic diversity





Each breed has a breedpack with genetic tests relevant for the breed

Designed by the Scientific Commission with help of the breedclub

➤ Genetic identification (ISAG 2020 and ISAG 2006)

Diseases:

- NCLA: Neuronal ceroid lipofuscinosis A
- PLL: Primary Lens Luxation
- ➤ PRA3 : Progressive retinal atrophy PRA3
- > RCD4: Progressive retinal atrophy rcd4

TIBETAN TERRIER BREEDPACK



Coat color genes:

➤ LocA : Agouti

➤ LocB : Black or Brown

➤ LocEx : Extension

➤ Lock : Dominant black

> LocS: White

> Raly: tan markings

Coat texture:

LocC : Curly coat

LocIC : Furnishing

→ 12 gene tests results + genetic identification for each dog

A practical tool for breeders





> NCLA: Neuronal ceroid lipofuscinosis A

Number of tested dogs	NCLA clear	NCLA carrier	NCLA affected
127	120	6	1

> PLL: Primary Lens Luxation

Number of tested dogs (genetic test)	PLL clear	PLL carrier	PLL affected	
127	103	24	0	

Number of tested dogs (clinical test)	PLL clear	PLL affected		
153	153	0		





➤ PRA3 : Progressive retinal atrophy - PRA3

Number of tested dogs	PRA3 clear	PRA3 carrier	PRA3 affected
115	115	0	0

> RCD4: Progressive retinal atrophy – rcd4

Number of tested dogs	rcd4 clear	rcd4 carrier	rcd4 affected
123	87	35	1

→ Would it be possible to compare with other countries?

TIBETAN TERRIER RESULTS IN FRANCE



LA SANTE

TERRIER TIBETAIN

GÈNES D'INTÉRÊT

	20	121	20	120	2	019	20	018	20	117
	Nbre	%	Nbre	%	Nbre	%	Nbre	%	Nbre	%
LocB-B/B	30	94%	9	90%	6	100%	1	100%	0	0%
LocB-B/b	2	6%	0	0%	0	0%	0	0%	0	0%
LocB-b/b	0	0%	0	0%	0	0%	0	0%	0	0%
LocB-B/b_b/b	0	0%	1	10%	0	0%	0	0%	0	0%
LocB-B/B_B/b_b/b	0	0%	0	0%	0	0%	0	0%	0	0%
TOTAL LocB	3	32	1	10		6		1.		0

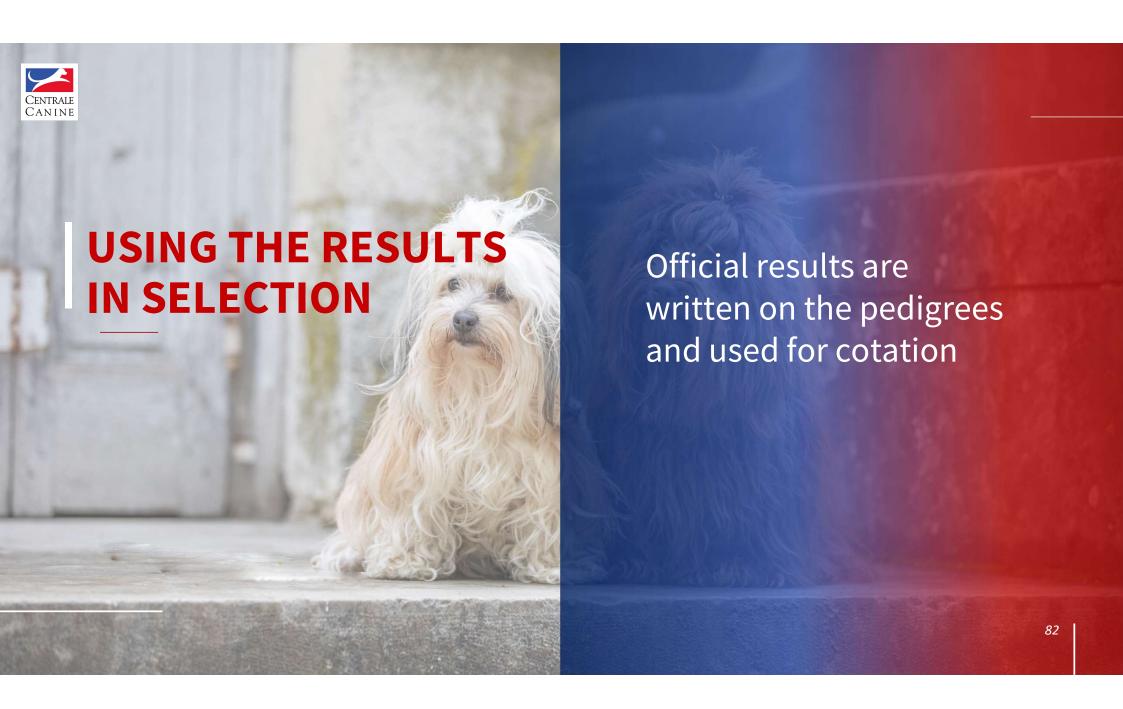
HETEROZYGOSITY



What is this rate?

- Reality of the inbreeding coefficient
- Should be as high as possible

Breed	Number of dogs tested	Mean of heterozygosity rate		
Berger australien	472	38%		
Chien de berger belge	246	37%		
Golden Retriever	216	31%		
Berger américain miniature	158	41%		
Staffordshire Bull terrier	158	32%		
Chien de berger des Shetland	154	33%		
Cocker spaniel anglais	129	32%		
Retriever du Labrador	129	33%		
Cavalier King Charles	97	26%		
Tibetan Terrier	20	36%		







Database

- Registering clinical and genetic results
- Data is collected through breeders, owners, breedclubs, vets
- Can be used for selection with displaying of information on our online database, but also for research purpose

Population data

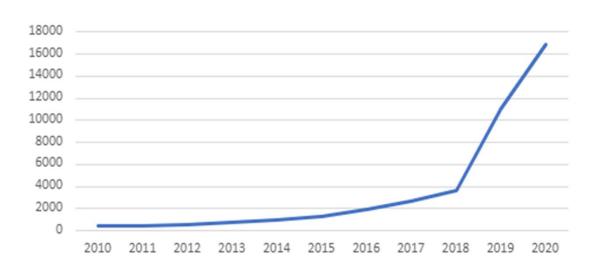
- Focus on diseases expressed in our population
- Identify new diseases in a breed
- Research projects to identify genes





- Free
- Registering the results is not mandatory
- → Engage in a positive communication about selection on health

Number of test results registered by year





REGISTERING SYSTEM

For each breed and each disease (and the associated mutation), the Scientific Commission determines the level:

Maladie suivie (important disease)

Results are on the pedigree and on LOF Select

Maladie sous surveillance (under surveillance)

→ Results are on LOF Select

Maladie émergente ou potentiellement émergente → (potentially emerging)

→ Results are not shown

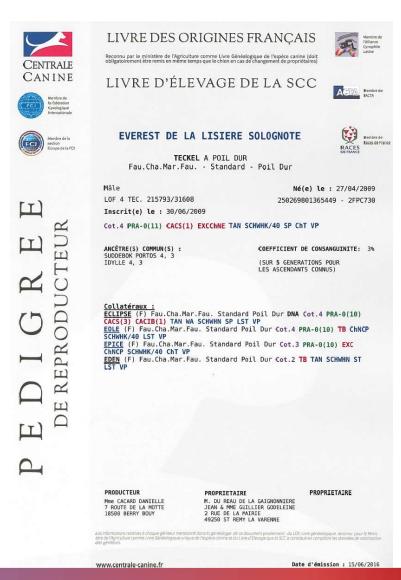


Registering a result does not mean it is shown

OUR PEDIGREE

The official document

- Only important diseases
- Gives all information at first glance

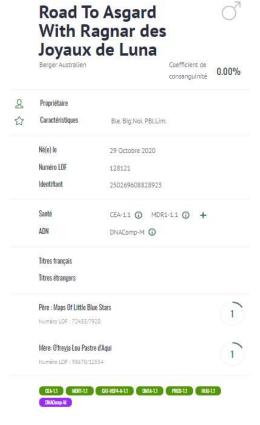




ONLINE DATABASE: LOF SELECT



- Find all test results (important and under surveillance diseases) online for all dogs
- Verify the identification and parentage compatibility
- Simulation of pedigrees

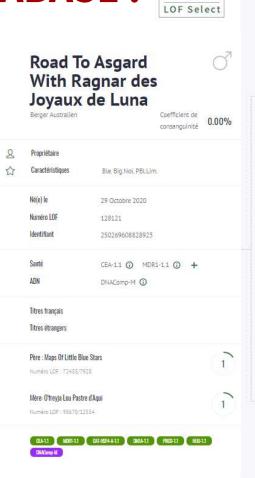


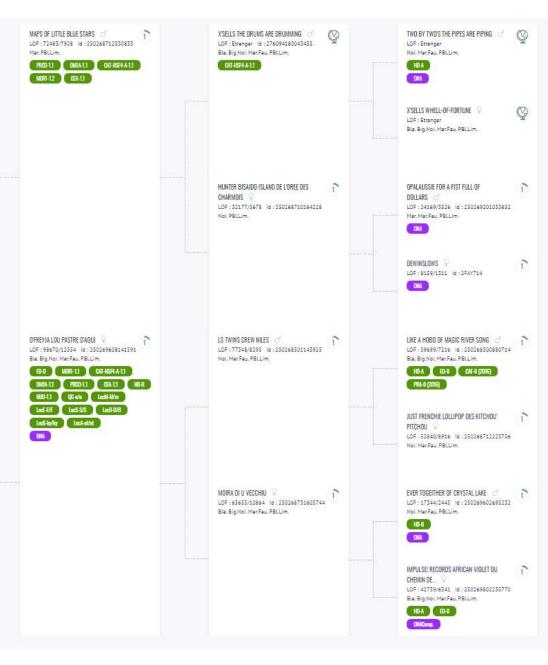


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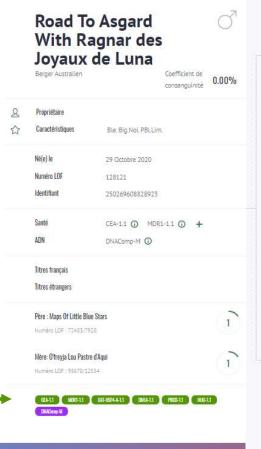


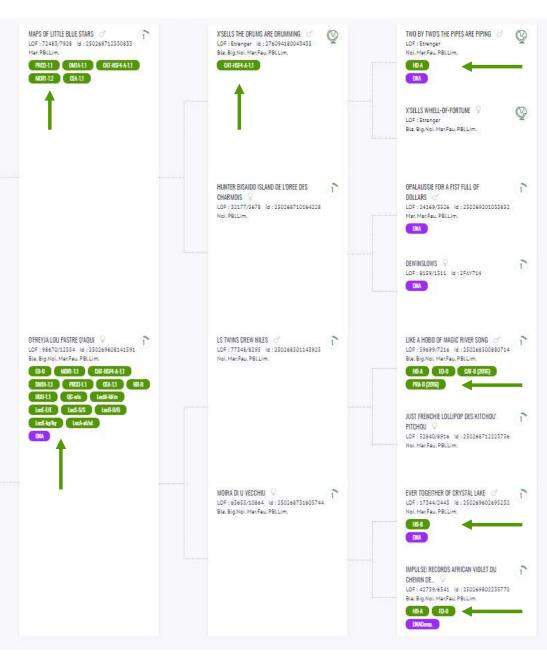
Genomics as an aid to selection – Tibetan Terrier Congress 2022

ONLINE DATABASE: LOF SELECT



- Find all test results (important and under surveillance diseases) online for all dogs
- Verify the identification and parentage compatibility
- Simulation of pedigrees



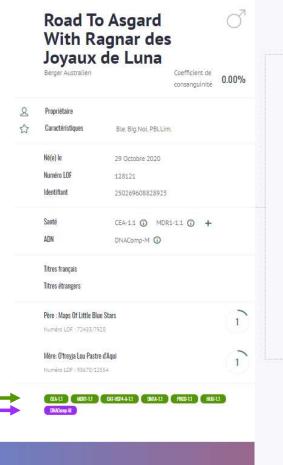


Genomics as an aid to selection – Tibetan Terrier Congress 2022

ONLINE DATABASE: LOF SELECT



- Find all test results (important and under surveillance diseases) online for all dogs
- Verify the identification and parentage compatibility
- Simulation of pedigrees





Genomics as an aid to selection – Tibetan Terrier Congress 2022

SELECTION GRID

Cotation from 1 to 6

Includes health test: clinical and genetic results

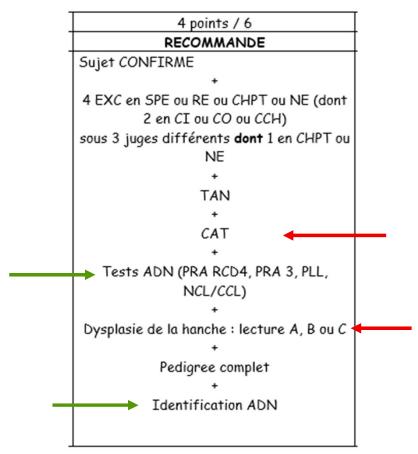
→ Gives the breeding value of a dog



Recommandé









CLEAR BY PARENTAGE

- When the parentage is genetically certified
- And the 2 parents are clear for a disease
- Then the offspring is automatically clear for this disease « clear by parentage »
- Calculated on 3 generations





Why?

- To ease the use of imported dogs
- To have a larger population to work on

Dog organizations





National Kennel Clubs

Vet organizations



- WSAVA World Small Animal Veterinary Association
- OFA Orthopedic Foundation for Animals





INTERNATIONAL CONSENSUS?

International Partnership for Dogs (IPFD)

Worldwide organization with:

- Breeders,
- Vets,
- Geneticists,
- Kennel Clubs,
- ..

Goals of IPFD

- Help harmonise the use of genetic tests
- HGTD Information pages on :
 - The labs who provide genetic tests
 - Which test is relevant for each breed





Genetic tests is a useful tool

It is worth the investment when we talk about breeding stock

Helps selection

BREED

Genomics (SNP) is the future of genetics







THANKS FOR YOUR ATTENTION!

Fleur-Marie Missant – <u>fleur-marie.missant@centrale-canine.fr</u>



Dr Daniel Combarros

Lecturer at the Veterinary school lof Toulouse

Itching: understanding it, treating it, prevent it

My Tibetan Terrier is itchy... is this atopic dermatitis?

Daniel Combarros, Dipl.ECVD

European Specialist in Veterinary Dermatology Service de dermatologie, Université de Toulouse, ENVT Infinity, Université de Toulouse, INSERM, ENVT







- 2021... call from Ms. Estru
 - Dermatological condition in Tibetan Terriers
 - Chronic issue and therapy
 - Worldwide problem



- Not many in Toulouse... other regions?
 - Call to colleagues
 - Itch, pododermatitis, otitis...
 - → Very predisposed to atopic dermatitis

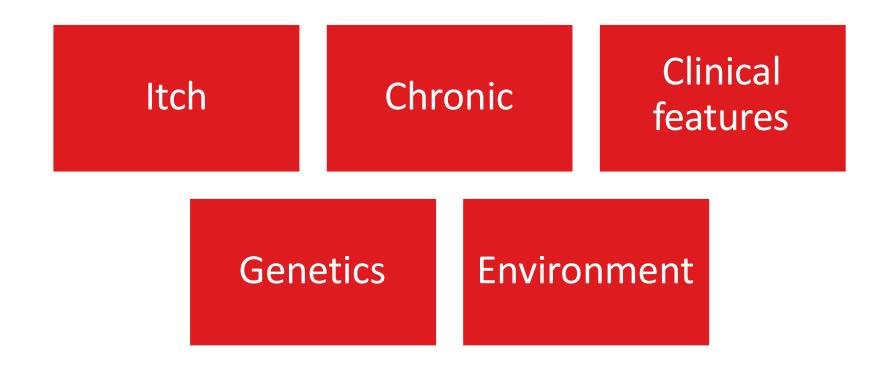


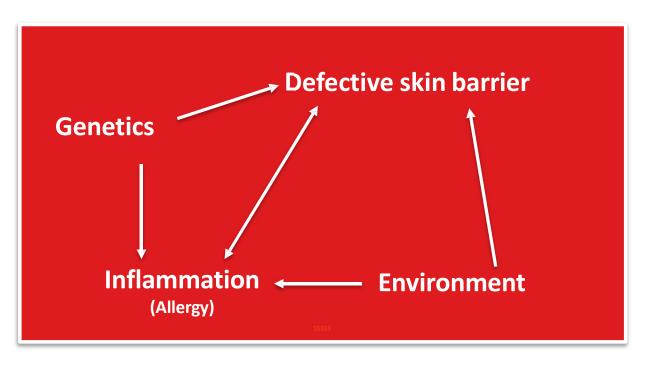
- 1 What is this atopic dermatitis?
- 2 Is my dog suffering from atopic dermatitis?
- 3 Can it be prevented?
- 4 What is the treatment of atopic dermatitis?

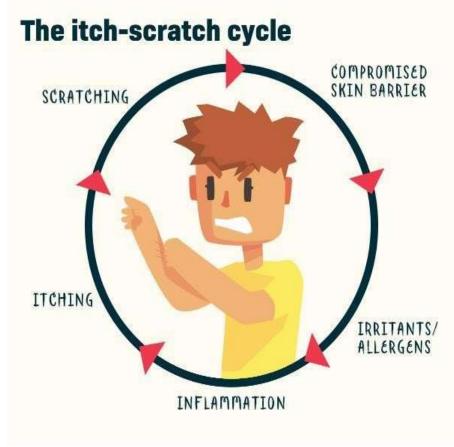
WHAT IS ATOPIC DERMATITIS?

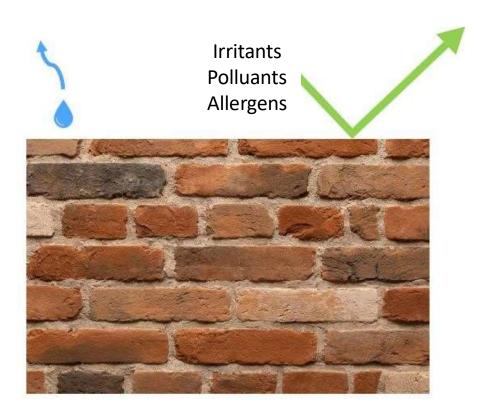


A common, chronic, genetically predisposed, inflammatory and pruritic (itch) skin disease with characteristic clinical features, commonly associated with the presence of antibodies against environmental allergens (allergies)

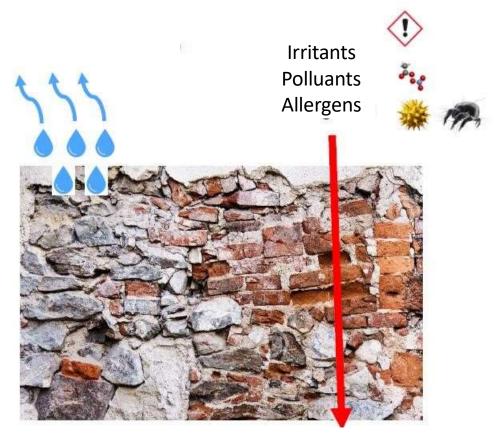








IMPERMEABLE Skin



Skin is **DRY** and **POROUS**

Environment influence

Reduced risk

Increased risk



Cities

High density



Rural areas



Countryside walks



Other animals

Dog











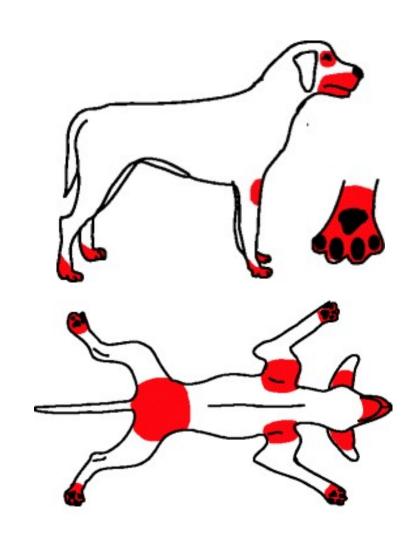
(Marsella et al, 2017)

2

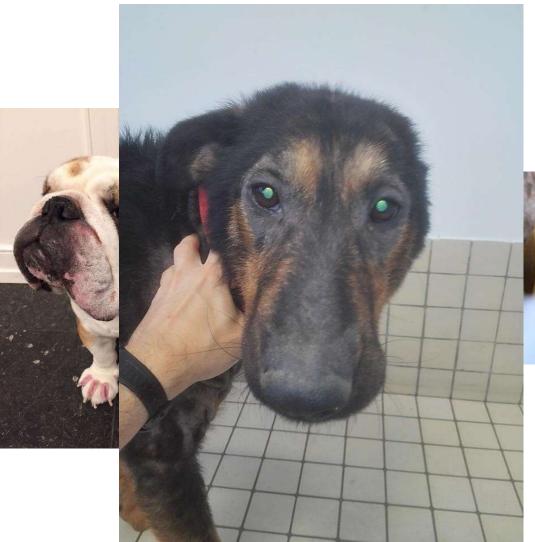
IS MY DOG SUFFERING FROM ATOPIC DERMATITIS?



- Probably yes if...
 - The itch started before 3 years of age
 - Initial itch without lesions
 - Affected front feet
 - Recurrent otitis
 - The itch is responsive to glucocorticoids
 - Dog lives mostly indoors
 - Non affected: dorsolumbar area, ear margins





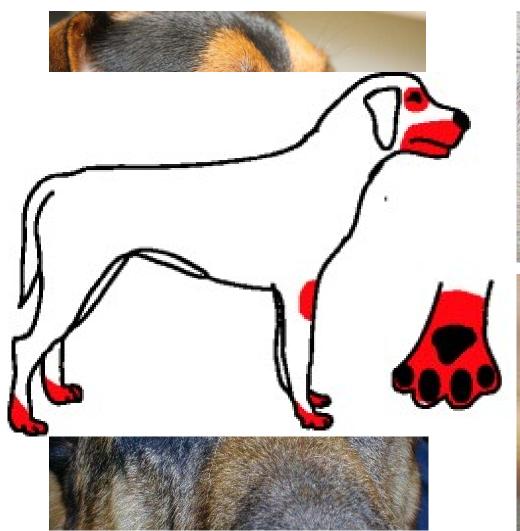


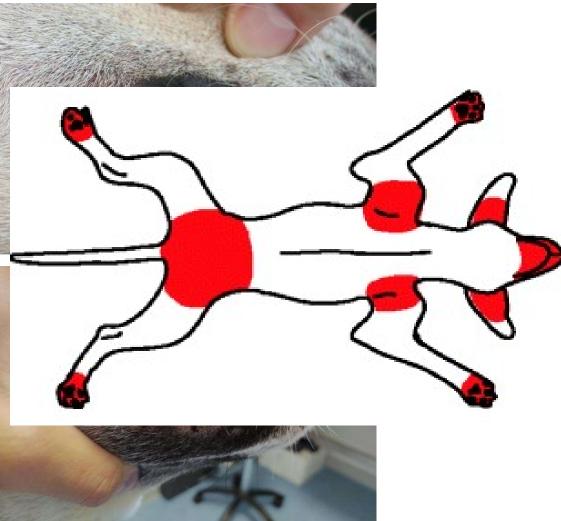












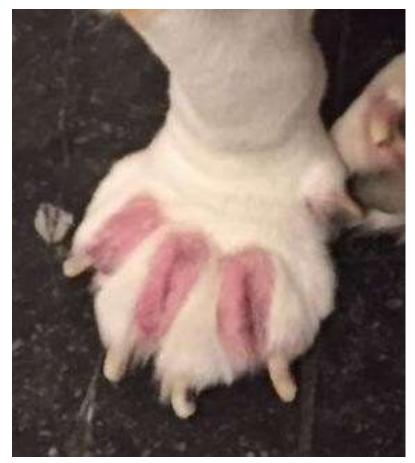
















Bacterial folliculitis

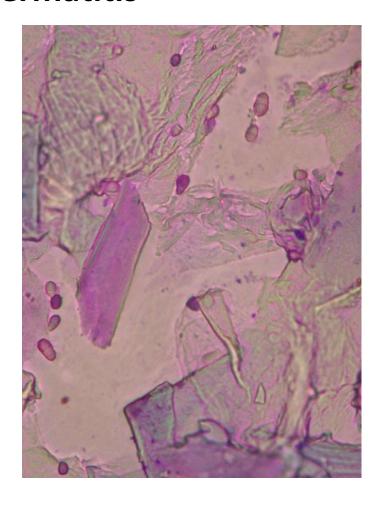


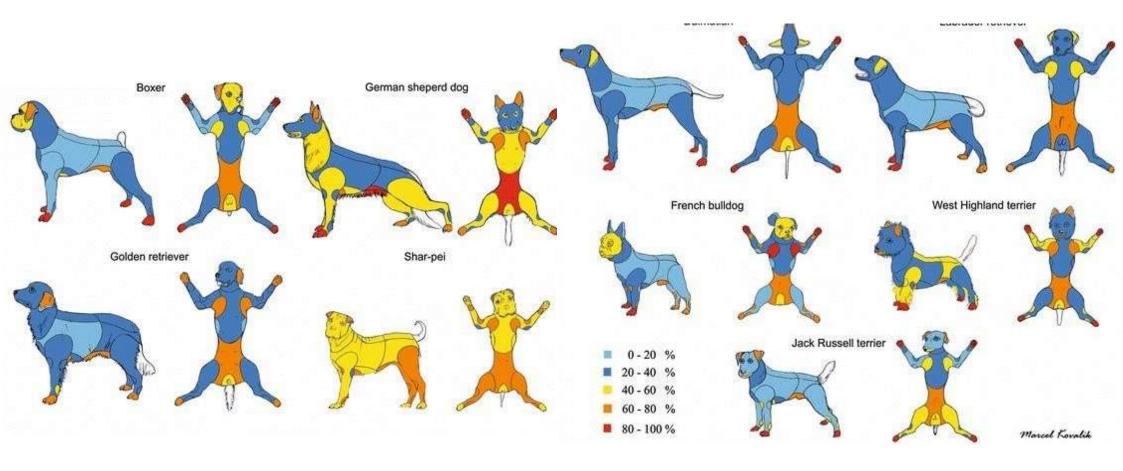
Bacterial overgrowth



Malassezia dermatitis







Otitis



Pododermatitis Otitis Malassezia

Sarcoptic mange (scabies)





Flea bite hypersensitivity





MSD Vet Manual

Zinc responsive dermatitits



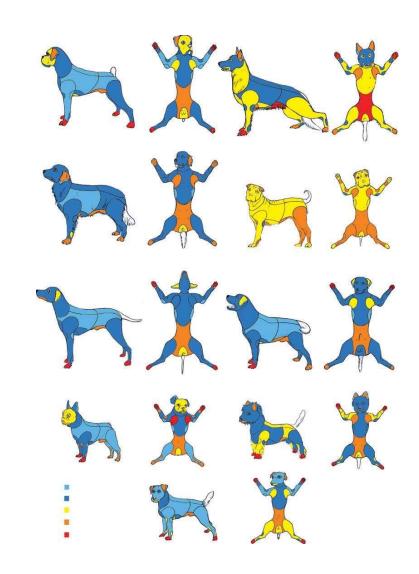


3

CANATOPIC DERMATITIS BE PREVENTED?



- Prevalence very high in some breeds → genetics
 - Heritability
 - 0.47 Labradors
 - 0.31 WHWT
- No single gene! Multigenetic disease...
 - Immunity response
 - TSLP R (several breeds)
 - PTPN22 (WHWT)
 - Skin barrier
 - PKP2 (GSD)





NO! AND PROBABLY THERE WILL NEVER BE!!

- No a single gene but many
- Gene combinations
- Different genes depending on breed
- Not a single study about genetics of AD in

• Tibetan terriers



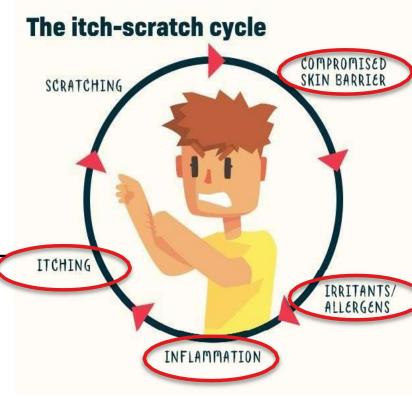
- What we know (study in labradors):
 - Risk of having an atopic dog is...
 - Greater if both parents have AD
 - Moderate if only one parent
 - Lowest if neither parent
- Excluding atopic dogs from breeding will decrease the prevalence
 - Progressively (asymptomatic dogs can carry susceptibility genes)
 - Problem → not possible if too many affected (French Bulldog)...

4

HOW IS ATOPIC DERMATITIS TREATED?



- CHRONIC life-long disease!
 - No cure!
 - Chronic treatment
 - Objective
 - Control the disease
 - Quality of life (dog, owner)
 - Minimal treatment
- Multifactorial disease → MULTIMODAL TREATMENT
 - Many treatment possibilities (no perfect one)
 - Combination
 - Each animal is different



Shampoos

- Reduce allergen concentration on skin
- Restore skin barrier moisturizer
- Treat/prevent skin infection

Flea prevention

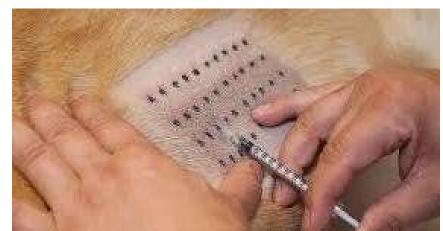
- Systematic! All year around
- If flea bites → flares/ destabilization!



- Find the allergen that trigger the disease
 - Food → hypoallergenic diets (no blood test!)
 - Environment
 - Blood tests
 - Intradermal tests



- If the environmental allergen is found
 - Immunotherapy: long-term injections
 - Calm down the immune system
 - ONLY SPECIFIC treatment



Control inflammation/itch

- Topical: Dermo-glucocorticoids
- Systemic:
 - Glucocorticoids
 - Ciclosporin (Atopica®, Cyclavance®, Modulis®)
 - Oclacitinib (Apoquel®)
 - Lokivetmab (Cytopoint®)











General principle → minimal effective dose

- Very frequent disease! (many breeds)
- Chronic, lifelong, non curable
- Very complex → defective skin barrier and hyper-reactive immune system
- No genetic test but possibility of excluding animals from breeding
- Many treatments available → multimodal → minimal effective dose





Multiplex Cytokine Analyses in Ear Canals of Dogs Suggest Involvement of IL-8 Chemokine in Atopic Otitis and Otodectic Mange—Preliminary Results

Line-Alice Lecru 1, Daniel Combarros 1,2, Fabien Moog 1, Lukrecija Marinovic 1, Jevgenija Kondratjeva 1, Nicolas Amalric 3, Charline Pressanti 1 and Marie Christine Cadiergues 1,2,*





Survey of cytokines on ocular surfaces of atopic dogs by

Veterinary Dermatology

multiplex analysis using two sampling methods - a pilot study

Charline Pressanti* † 60, Elodie Ravailhe*, Jessie Castellote-Brun* 60, Nicolas Amalric§ 60, Line-Alice Lecru* (5), Jevgenija Kondratjeva* (6), Fabien Moog* (6), Daniel Combarros*+ (6), Jean-Yves Douet*:

> Refined Immunochemical Characterization in Healthy Dog Skin of the Epidermal Cornification Proteins, Filaggrin, and Corneodesmosin

Clinical Guidelines for the Use of Antipruritic Drugs in the Control of the Most Frequent Pruritic Skin Diseases in Dogs

Vincent Bruet 1 , Marion Mosca 2 , Amaury Briand 3 0, Patrick Bourdeau 4 , Didier Pin 2 0, Noëlle Cochet-Faivre 3,5 and Marie-Christine Cadiergues 6,7,*

REVIEW

a OPEN AG

Update on canine filaggrin: a review

Open Acce.

Daniel Combarros^{a,b} (D), Marie-Christine Cadiergues^{a,b} (D) and Michel Simon^a (D)



RESEARCH ARTICLE

Non-controlled, open-label clinical trial to assess the effectiveness of a dietetic food on pruritus and dermatologic scoring in atopic dogs

Angela Witzel-Rollins^{1†}, Maryanne Murphy¹, Iveta Becvarova², Stephen R. Werre³, Marie-Christine Cadierques⁴ and Hein Meyer²



Veterinary Dermatology

Vet Dermatol 2021; 32: 625-e167

DOI: 10.1111/vde.13010

Survey of cytokines on ocular surfaces of atopic dogs by multiplex analysis using two sampling methods - a pilot study

Charline Pressanti* 1 (a), Elodie Ravailhe*, Jessie Castellote-Brun* (b), Nicolas Amalric§ (c), Line-Alice Lecru* (6), Jevgenija Kondratjeva* (6), Fabien Moog* (6), Daniel Combarros* (7) Jean-Yves Douet** : 6 and Marie Christine Cadiergues** † 6



Dermatology service of the National Veterinary

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Marie-Christine Cadiergues

Charline Pressanti

Daniel Combarros

Fabien Moog
Jevgenija Kondratjeva
Mirabella Dumitrache
Damien Banuls
Maria-Antonia Salva
Jessie Brun







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European Specialist in Veterinary Dermatology

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Round table - Discussion

Tibetan terrier World Congress



Mark James / Glenn Davies Waterley kennel

Tibetan terriers, A passion, knowledge and understanding



Dr Mike Tempest Mikudi kennel

An analysis of the 2019 genetics paper and what it means for the breed

ADDRESSING TOPICAL ISSUES

Analysis of the 2019 scientific paper

"POPULATION STRUCTURE AND GENETIC HISTORY OF TIBETAN TERRIERS"

by

M Janeš, M Zorc, V Cubric-Curik, I Curik and P Dovc (University of Zagreb, Croatia and University of Ljubljana, Slovenia)

Genetics Selection Evolution (2019) 51:79 https://doi.org.10.1186/s12711-019-0520-4

What did the study do?

- It tested if the original TT belonged to a group of ancient dog breeds of Asian origin
- It tested if the TT belonged to the group of terrier breeds
- It compared the current Western and Native populations
 - It compared two lineages: 'Lamleh' and 'Luneville'

Some abbreviations used in the study

- TTLA = 'Lamleh'
- TTLU = 'Luneville'
- TT(WP) = Western Population = TTLA + TTLU
 - TTNA = Native population in Tibet
- TTF1 = 1st generation cross = TTNA (50%NA) x TTLA (50%LA)
- TTBC2 = 2nd generation backcross = TTF1 (25%NA) x TTLA (75%LA)
- TTBC3 = 3rd generation backcross = TTBC2 (12½%NA) x TTLA (87 ½%)

How many animals were DNA sampled in the study?

- TTLA = 20 at dog shows or directly by breeders/owners
- TTLU = 4 at dog shows or directly by breeders/owners
 - TT(WP) = 24 registered with FCI
 - TTNA = 22 at 22 locations in Tibet
 - TTF1 = 8
 - TTBC2 = 6
 - TTBC3 = 4
 - TOTAL = 64

How was the study done?

Employed several genetic analytical techniques

Main two techniques were:

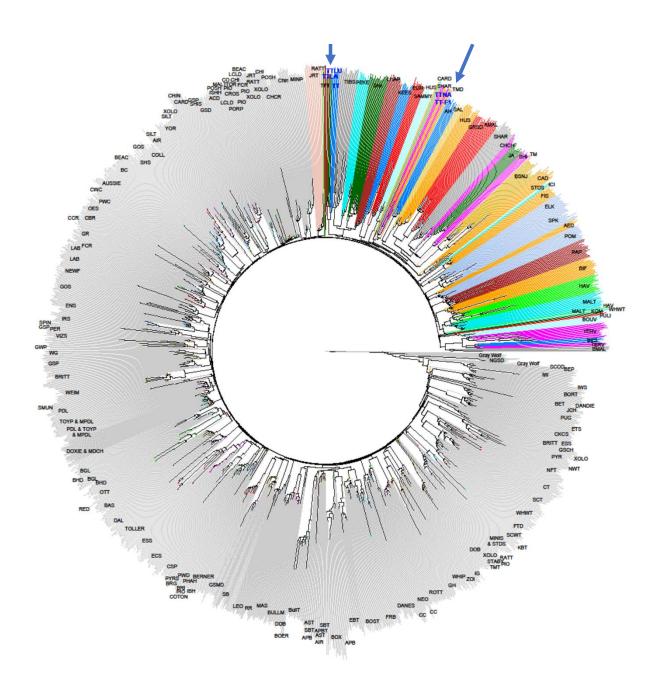
(1) Neighbor-joining tree

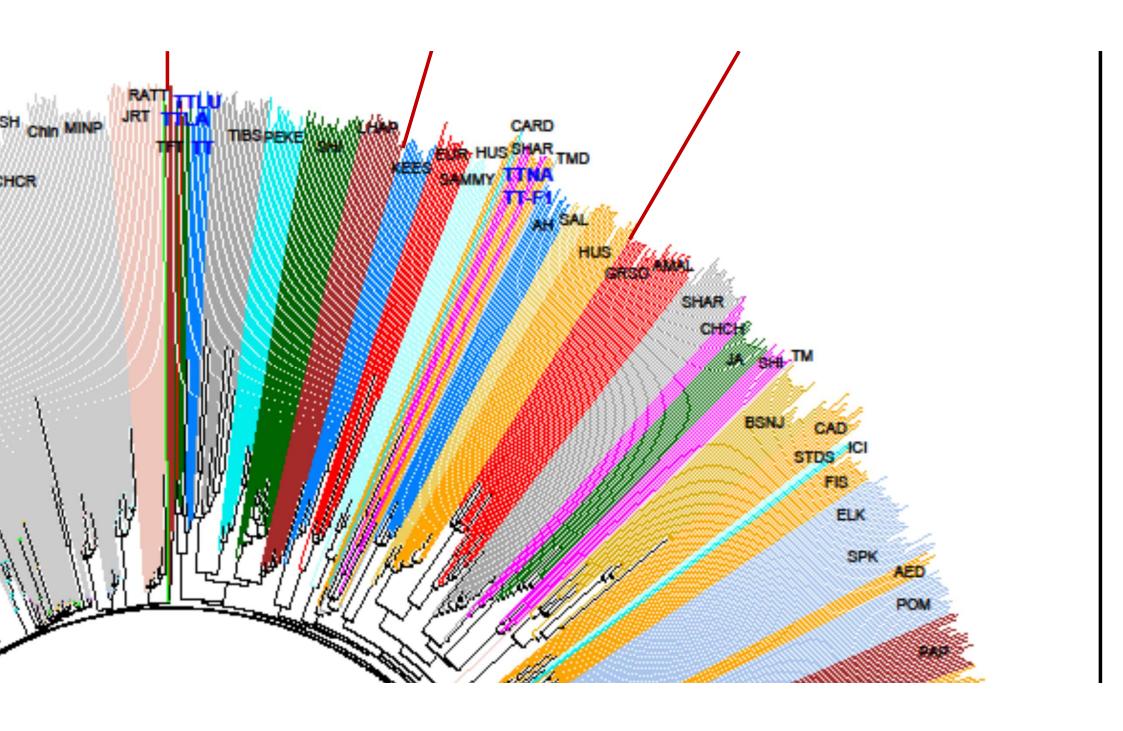
(2) NeighborNet

(1) Neighbor-joining tree

Computes genetic distances between 161 dog breeds/strains

Where do TTs fit in?





Results from (1) Neighbor-joining tree

TTs were in two clusters

TTNA and TTF1 (50% NA) are grouped with a Cluster of Ancient Asian Dog Breeds which included AH, SAL, SAMMY, HUS (2)

and TTLA, TTLU, TTWP are grouped in a Tibetan Companion Dog Cluster which included TIBS, PEKE, SHI, LHAP

Results from (1) Neighbor-joining tree

Most importantly:

There was no genetic distance between TTLA & TTLU LA & LU lineages are genetically similar

There was a small genetic distance between TTWP & TTNA Current WP is slightly different from current NA

Results from (1) Neighbor-joining tree

BUT

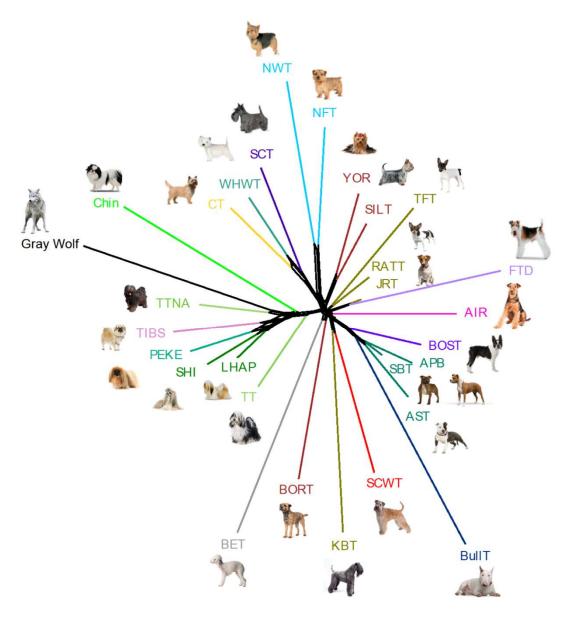
TTWP (TTLA + TTLU)
showed some relationship with the
group of Terrier breeds

TTWP showed some sporadic contacts may have occurred between TTWP and some Terrier breeds during the last century

(2) NeighborNet

Computed phylogenetic relationships between TTs and 27 dog breeds and Grey Wolf

Where do TTs fit in?



Results from (2) NeighborNet

This clearly showed Terrier breeds formed a group on the other side of the network separate from all the TT. This confirmed that TTs are not Terriers.

It also showed that TTNA branch is closer to the Grey Wolf than any other breed.

The TT is a very ancient breed.

BUT the edges between TTNA and TIBS, PEKE, SHI and LHAP indicate hybridization events between them.

What answers did the study produce?

- Does the native TT belong to a group of ancient dog breeds of Asian origin? YES
 - Does the TT belong to the group of terrier breeds?
 NO
- How do the current Western and Native populations compare?
 SLIGHTLY DIFFERENT
 - How do the two lineages 'Lamleh' and 'Luneville' compare?
 NO GENTIC DIFFERENCE BETWEEN THEM

Why are WP and NA slightly different?

- NA has been subject to 'genetic drift' away from from the NA population that provided the exports of 100 years ago.
 - WP experienced a 'bottle-neck' that made it more uniform than NA.
 - WP was pedigree recorded and selectively bred, NA was not pedigree recorded and was randomly bred.
 - WP was restricted to pedigree registered individuals.
 - NA population was open for admixtures with phenotypically similar individuals from outside the breed

What are the implications for the breed?

To recognise now that the science tells us:

- "the WP had some sporadic contacts with Terrier breeds"
- "the NA had/has hybridization events with TIBS, PEKE, SHI and LHAP" (street dogs)
- "There has been significant gene flow from the NA population to both LA and LU lineages"

What are the implications for the breed?

The fraction of the NA genome containing homozygous regions is smaller, & heterozygous regions larger, than in the WP genome i.e. the NA population is genetically more variable than the WP.

The NA is an important genetic resource for preserving the original gene pool, and represents a 'back-up' population for the WP.

NA could be used to increase genetic diversity in the WP.

BUT care must be taken in selecting Native TTs that have not been subject to hybridisation events in Tibet.

What are the implications for the breed?

To recognise the that:

- For 'Lamlehs' "Dogs brought into the UK up until 1951 by other owners were intermingled by Dr Greig with her original imports so that today it is impossible to trace any living TT containing only Dr Greig's own original lines" (Angela Mulliner, 1977)
 - For 'Lunevilles' they were founded on 'Lamlehs'

	KALA KAH OF LAMLEH	LUN CHREE OF LAMLEH	CHRYS-SAN OF LAMLEH
			LIT-LUN OF LAMLEH
		KAH-NA OF LAMLEH	KALA KHRIS OF LAMLEH
			ZANA OF LATMAH
	LUNEVILLE LADY PENELOPE	TROJAN KYNOS	UNKNOWN
			UNKNOWN
		PRINCESS AUREUS	PA-SANG OF LAMLEH
			PRINCESS CHAN

LUNEVILLE PRINCE KHAN

Major Conclusion

I presented pedigree information at the TT World Congress in the UK in 2017 to answer the question:

"Lamleh and Luneville, Never the Twain Shall Meet?" and I showed from pedigrees that they had met a long time ago.

Now we have had in 2019 scientific information confirming that Lamleh and Luneville are genetically basically the same.

WE ARE ONE



Round table Standards and question about the breed Brian Harris – Mike Tempest – Mark James - Sabine Schiratti - Lydie Estru – Gauthier Lequain

Voilà, c'est fini.....

Thank you!



Hope you had a nice TT World Congress.

It was such a pleasure to welcome you.

Rendez-vous au prochain congrès!