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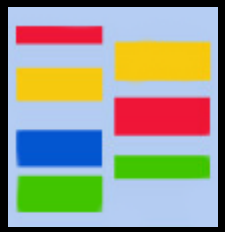
MHC associations of myositis in Hungarian Vizsla dog

Lorna Kennedy



Centre for Integrated Genomic Medical Research,
Manchester, UK

Why dogs?!?!

1 in 10 people in the UK own a dog
(that's about 6 million dogs!!) How many worldwide?

Large investment in working dogs

- Guide dogs, hearing dogs
- Farm dogs, drug sniffers
- Locating earthquake victims
- Detecting cancer, epilepsy
- heart attacks
  - Health care, insurance
  - Pet food

Advantages of the dog as a model

Medical knowledge about dogs:
  second only to humans!

Dog genome sequenced in 2005

Many genes very similar to human genes

Causal gene mutations for many monogenic canine diseases have been identified.

can be traced by synteny to human genome

Dogs as a model for complex disease

Many different breeds (>400)

- subject to intense selection for particular traits e.g. short legs, some bottlenecks: eg 2nd world war

Each breed is genetically distinct

Within breed very homogeneous

Complex diseases: may be subtypes, but within breed, disease likely to be same

100 cases/100 controls for GWAS, not 1000s

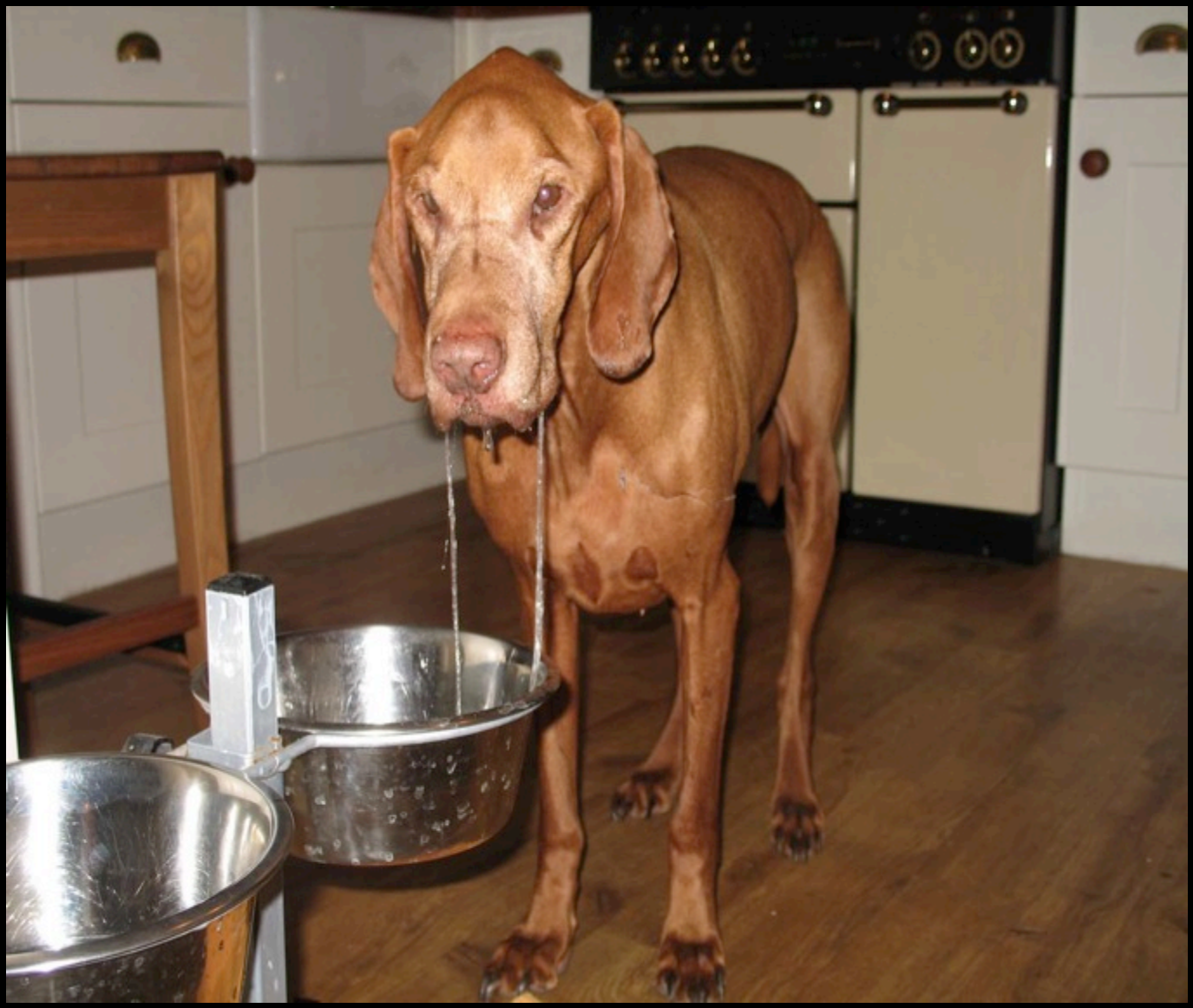
study same diseas/different genetic backgrounds

Canine myositis in Hungarian Vizslas

- A breed specific polymyositis is frequently observed in the Hungarian Vizsla.
- Affected dogs present with difficulty eating and drinking, regurgitation, and sialorrhea.
- Possible masticatory muscle atrophy and exercise intolerance
- Clinical response to immunosuppressive therapies points to an immune-mediated aetiology.
- Clinical and histological similarities with the immune-mediated myopathies observed in humans.
- MHC class II associations reported in the human conditions.

Affected dogs with megaesophagus – in "Bailey chair" to aid swallowing

Affected dog with sialorrhea: drooling!



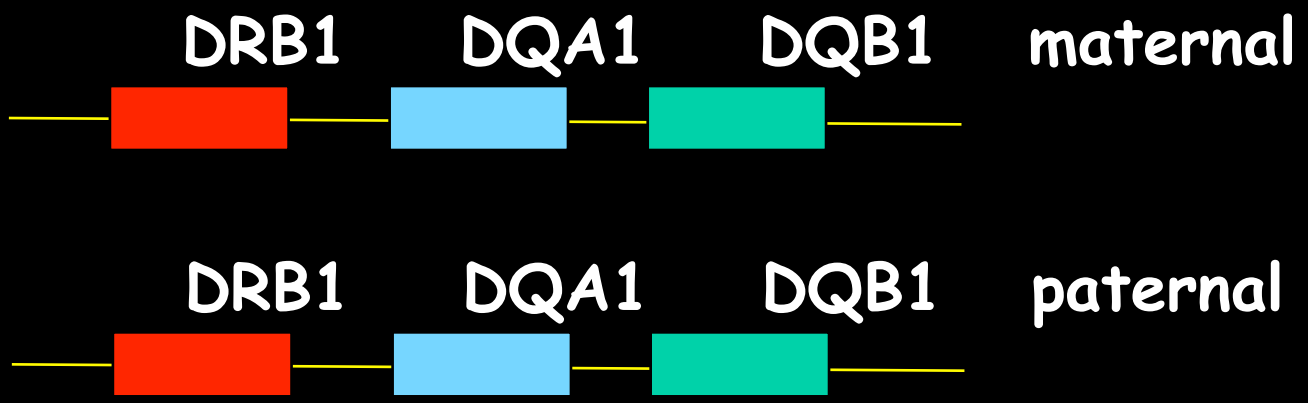
CIGMR

Canine Major Histocompatibility Complex

MHC genes and haplotypes

Inherited as sets or "haplotypes"
one from each parent: two in total

Co-dominant expression



N.B. No DP expressed in dogs

Canine MHC - DLA: very variable

Alleles and haplotypes in the domestic dog: 15,500 dogs from <200 breeds

Gene	No of alleles
DRB1	302
DQA1	39
DQB1	155
3 locus haplotypes	>300

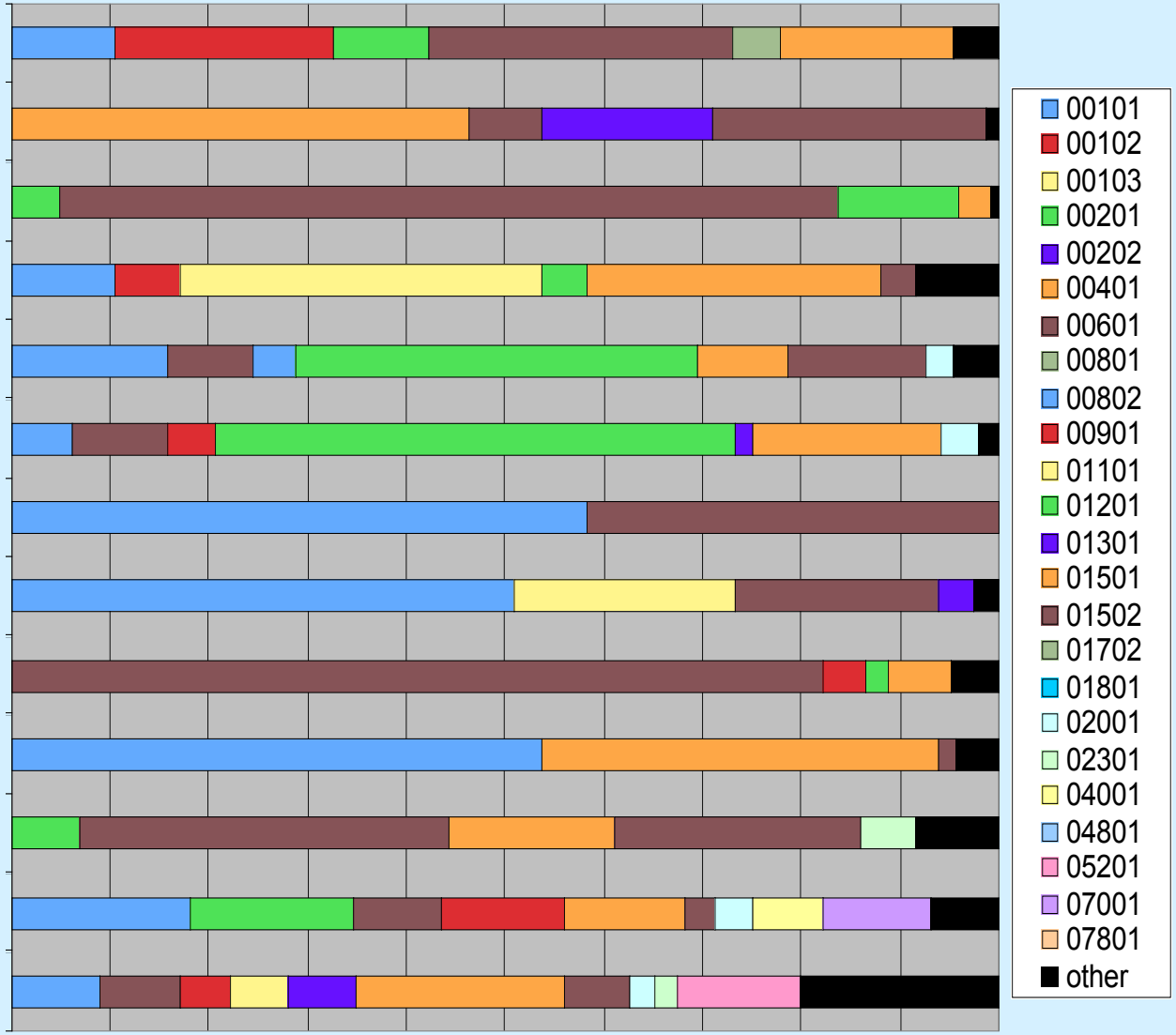
Variable breed distribution

Average per breed: 5-7 haplotypes

35% pedigree dogs are homozygous for MHC

DLA-DRB1 alleles in some breeds

n	
115	Beagle
170	Boxer
321	Doberman
327	German shepherd dog
816	Labrador (Retriever)
381	Retriever (Golden)
43	Rottweiler
73	Setter (English)
151	Spaniel (Cocker)
228	Terrier (Westie)
291	Terrier (Yorkshire)
177	Husky
109	Mongrel (Brazilian)



MHC diversity in breeds

Intrabreed

- some breeds have few alleles and haplotypes
- most breeds have 4-5 frequent haplotypes
- no breed has all known alleles/haplotypes

Interbreed

- some alleles and haplotypes are only found in a few breeds - "restricted"
- other alleles and haplotypes in many breeds

MHC associations with autoimmune diseases

Identified for:

Diabetes, Hypothyroid disease, IMHA, SLO, SLE, Addison's Disease, Meningiocephalitis,

Anal furunculosis, Chronic hepatitis, Pancreatitis

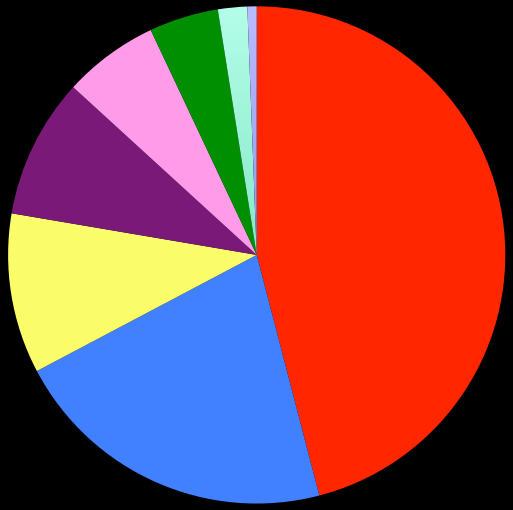
Different breeds can have different associations

Same haplotype can be associated with several diseases

MHC haplotypes in Hungarian Vizslas

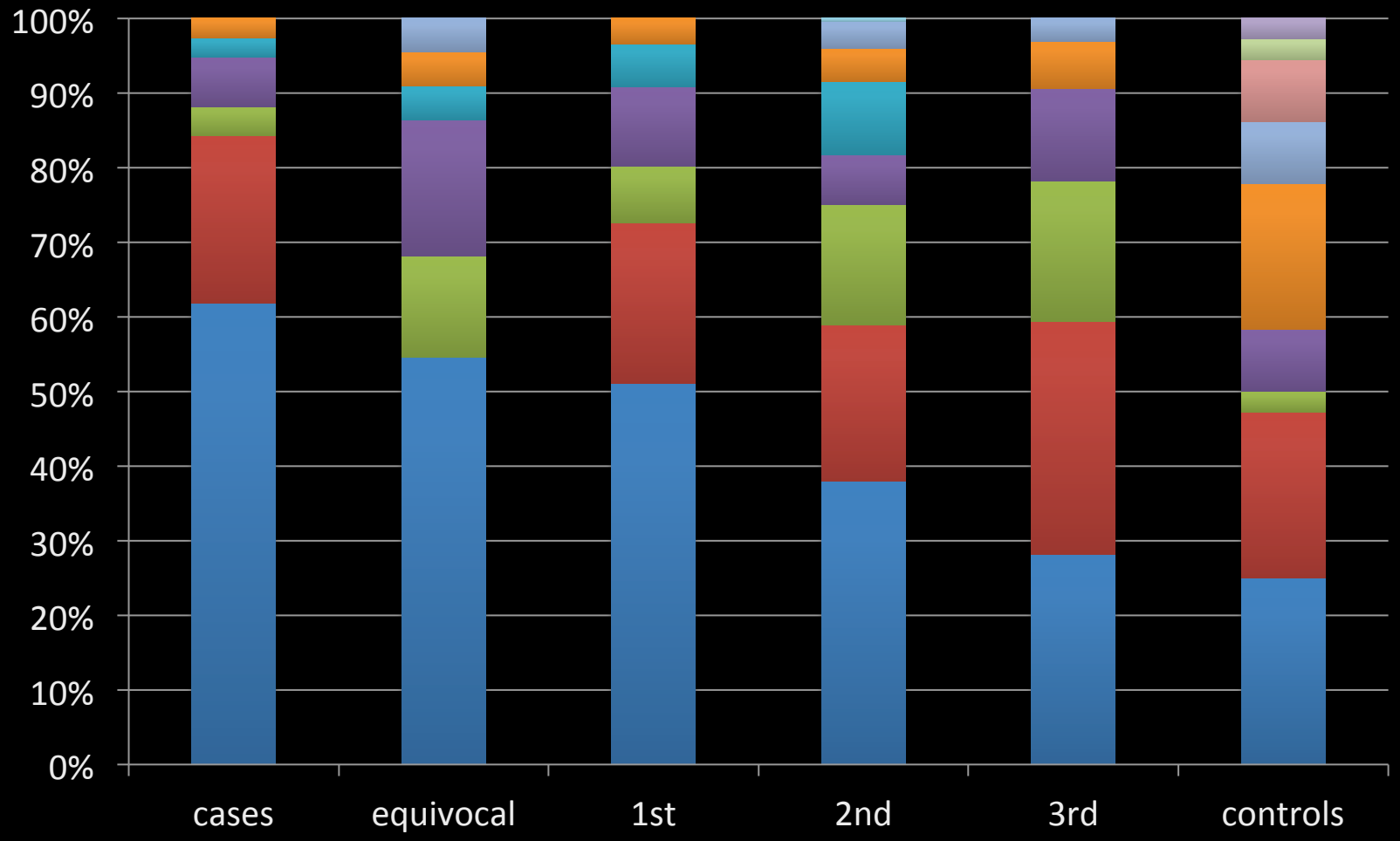
Eight different haplotypes

One very frequent (46%)
One frequent (21%)
Two less frequent (10%)
Four others (<6%)



Myositis risk haplotype

Haplotype frequencies by group



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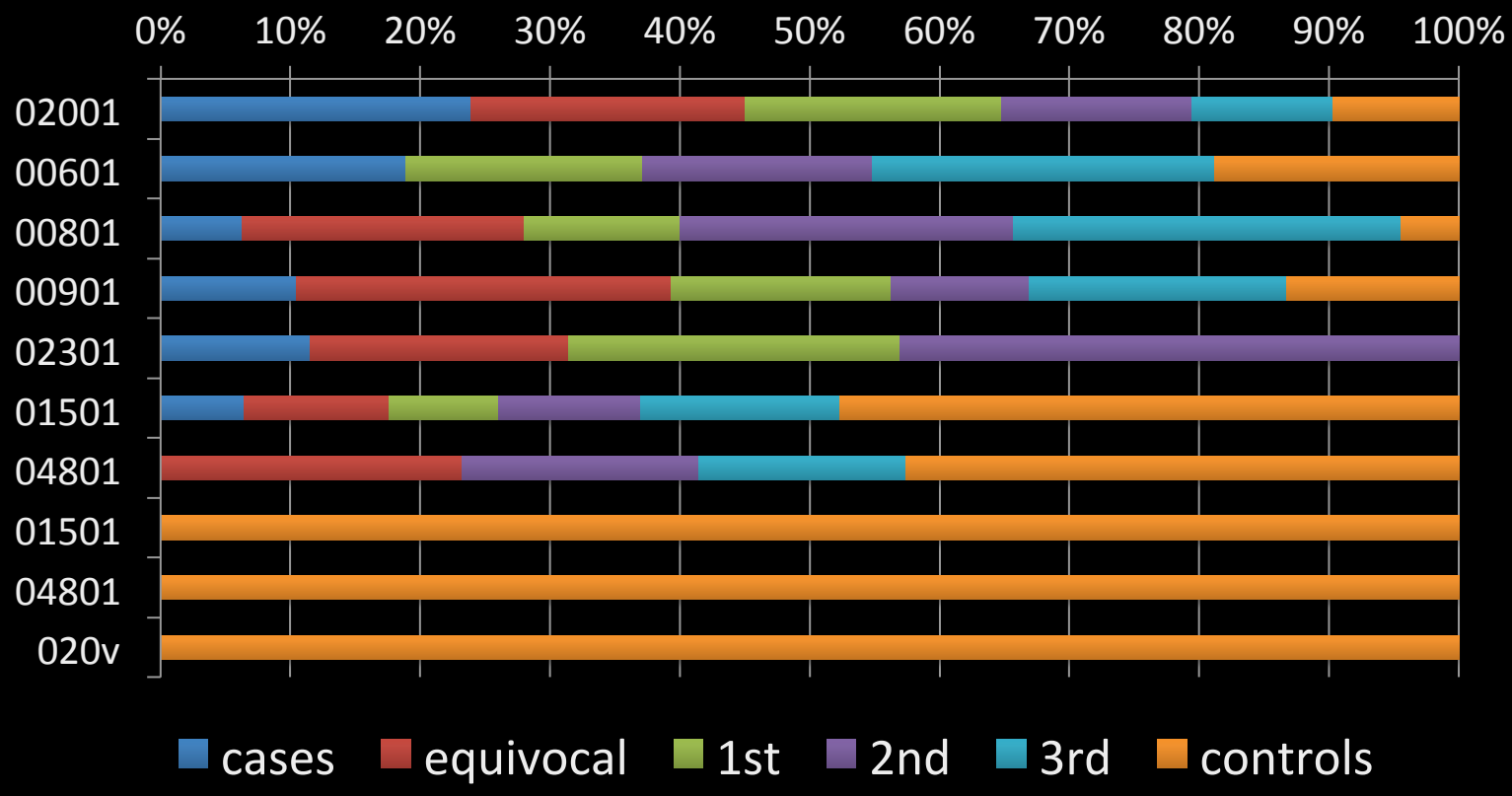
Distribution of groups by haplotype



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DLA haplotypes found in Hungarian Vizsla n=341

DLA	DRB1	DQA1	DQB1	%	Disease risk
1	02001	00401	01303	45.9	Canine myositis in Vizslas Also with immune diseases in Saluki Protective SLO in Gordon setters
2	00601	005011	00701	21.3	(IMHA; in other breeds)
3	00801	00301	00401	10.4	
4	00901	00101	008011	9.1	(Diabetes, RA; in other breeds)
5	02301	00301	00501	6.2	
6	01501	00601	02301	4.5	(Addisons; in NSDTR)
7	04801	00101	008011	1.9	
8	01501	nt	059v	0.6	Only found in vizslas from USA

SLO = Symmetrical Lupoid Onychodystrophy

An aside, for breeders!!!
How should we use MHC data?

Some evidence that homozygous individuals are slightly less able to respond to infection

"heterozygous advantage"

Some evidence that (human) couples who are both homozygous for the same MHC haplotype are at increased risk of spontaneous abortion…….

So maybe we should avoid mating identically MHC homozygous dogs

MUCH MORE important to not mate affected dogs, or those with affected 1st degree relatives

Take home messages

Strong MHC association
with myositis in the Vizsla

Future work: GWAS

For breeders:

DLA results should not be used as the only tool for mate selection

A genetic test will need

many more dogs of known disease status to be tested to identify relative contribution of different genes

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Pictures: Di Addicott

Canine myositis in Hungarian Vizslas

- Masticatory muscle myositis (MMM)
- Mean age of onset 2.3 years (range 0.2–8.8 years)
- Slightly more male dogs
- The most consistent clinical signs are dysphagia and regurgitation (due to tongue, pharyngeal and oesophageal dysfunction; and masticatory muscle atrophy)
- A marked elevation in muscle enzymes was an indicator of disease, but Vizsla Polymyositis could not be ruled out if muscle enzymes were normal