Identifying genetic markers for myositis in the Hungarian Vizsla

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Complex Diseases

Combination of

many genes (~~up to 40~~ LOTS!)

and

non-genetic factors (environmental triggers)

e.g. a viral infection, vaccinations, diet?

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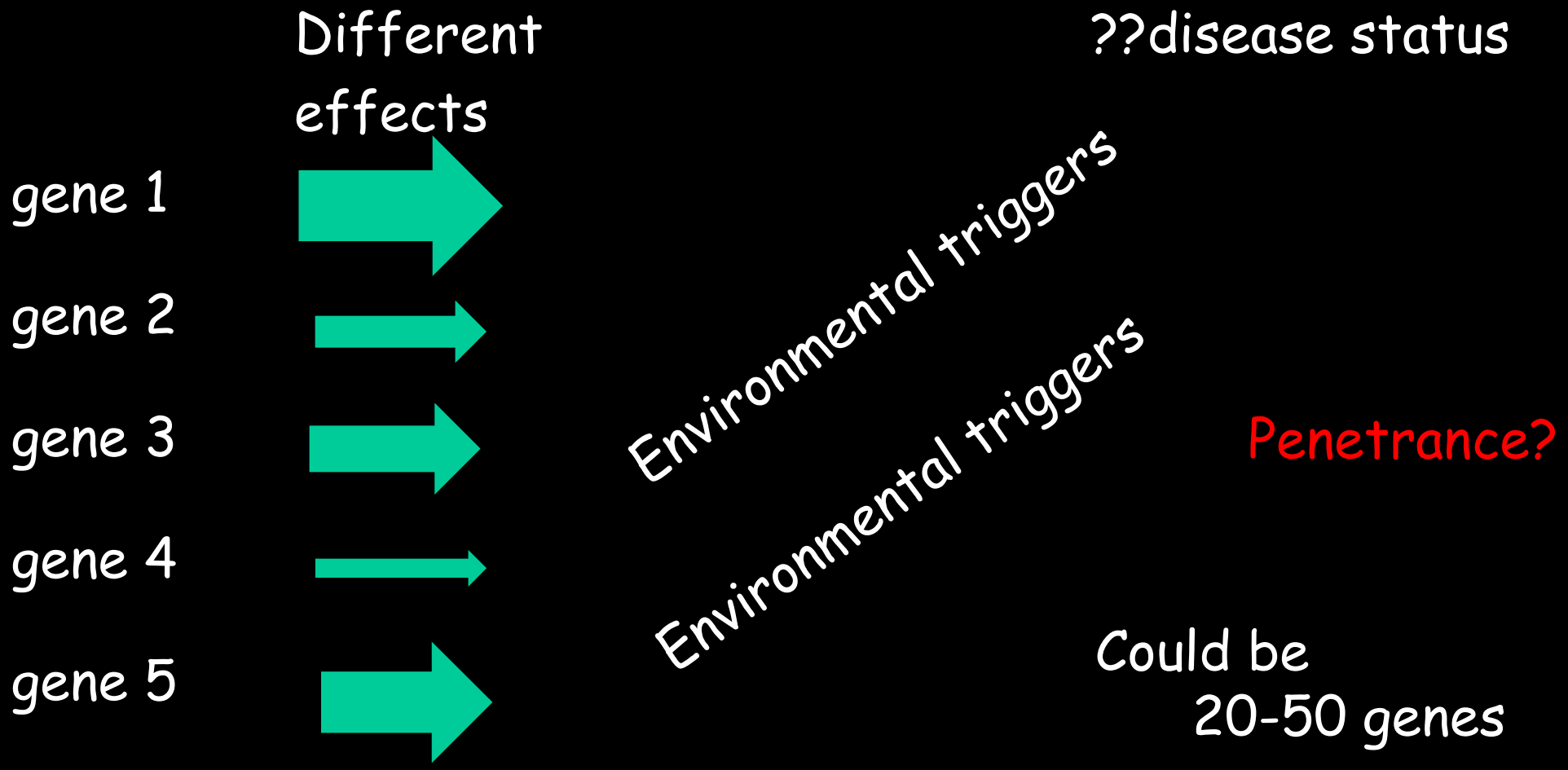
Disease status is a combination of genes and environment, so we cannot be certain of status with genes alone



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So why are we interested in the Major Histocompatibility Complex (MHC) in dogs?

- known to have the largest genetic effect on susceptibility in autoimmune diseases in man

What does the MHC do?

Proteins on the cell surface

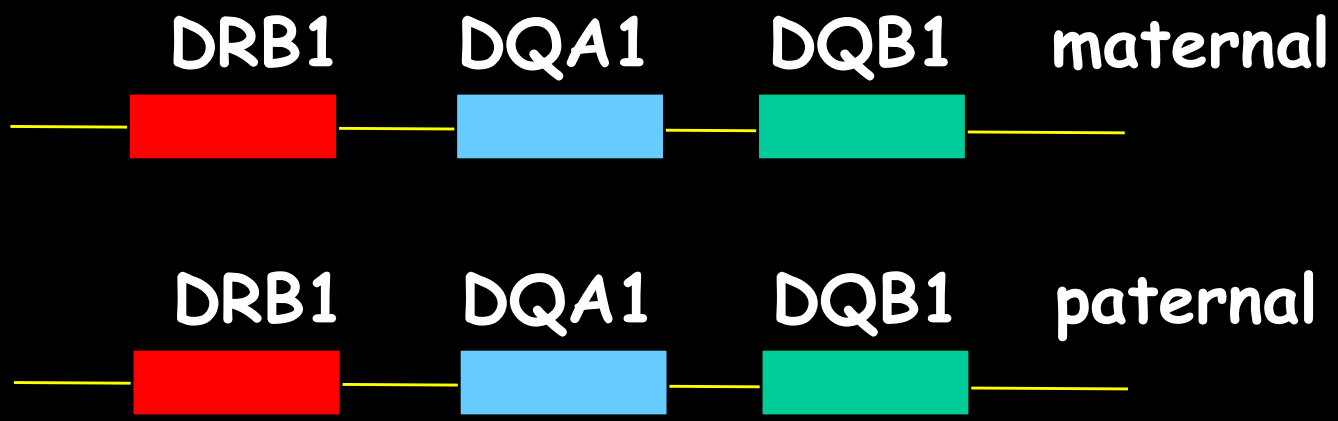
these regulate the immune response:

- response to infection, virus, bacteria
- disease susceptibility/resistance

and help the body to distinguish “self” from “non-self” (e.g. transplantation)

MHC genes and haplotypes

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



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

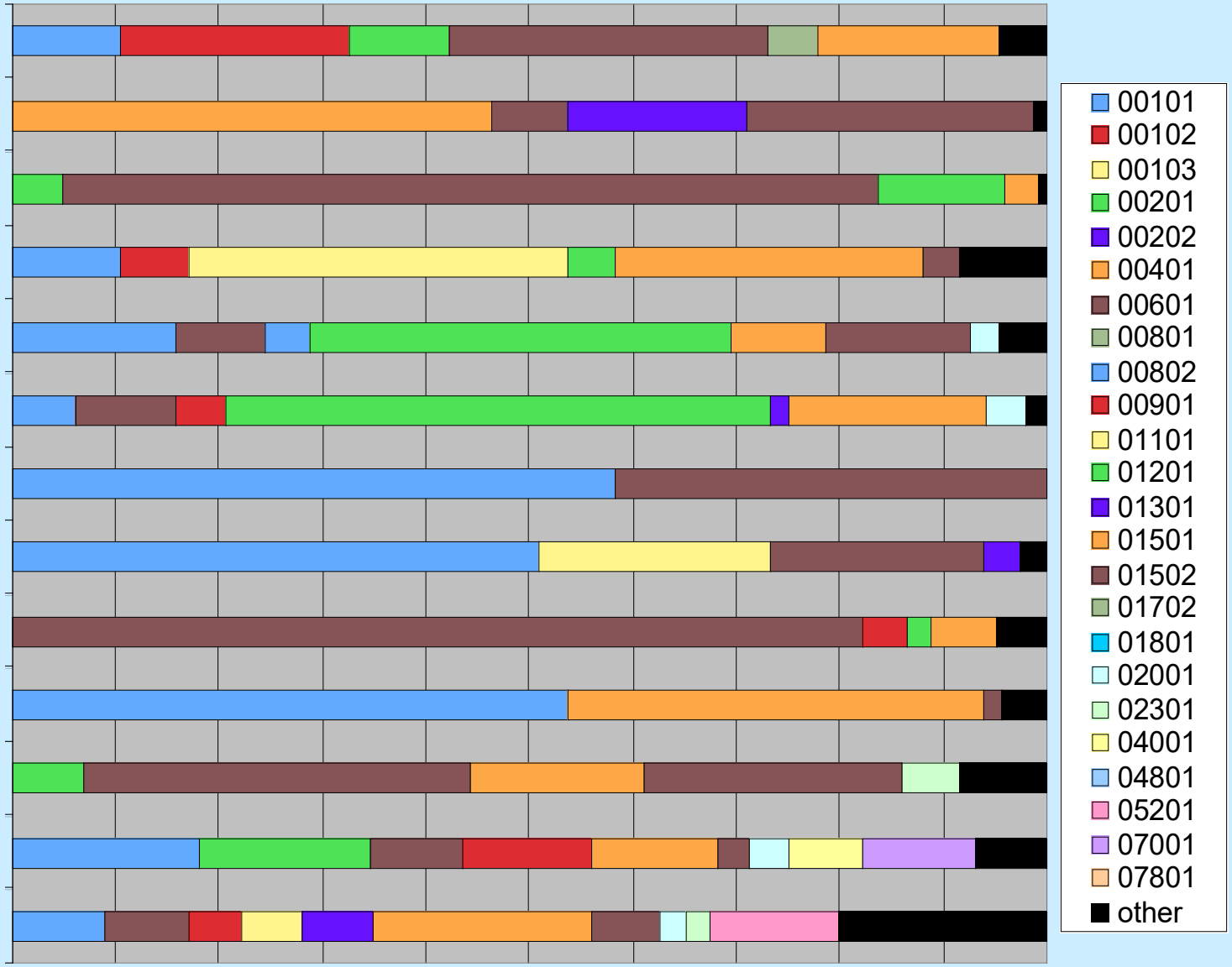
Variable breed distribution

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 canine autoimmune diseases

Identified for:

Diabetes, Hypothyroid disease, myositis, 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 different diseases

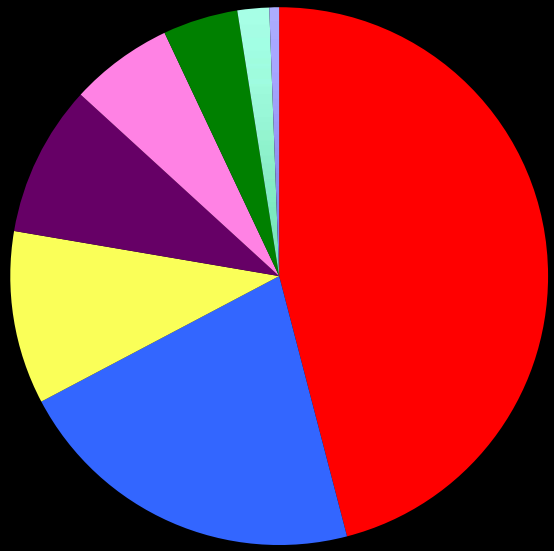
Canine myositis in Hungarian Vizslas

- 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
- The response to treatment with steroids suggests an immune-mediated origin.
- Clinical and histological similarities with the immune-mediated myopathies observed in humans.
- MHC class II associations reported in the human conditions.

MHC haplotypes in Hungarian Vizslas

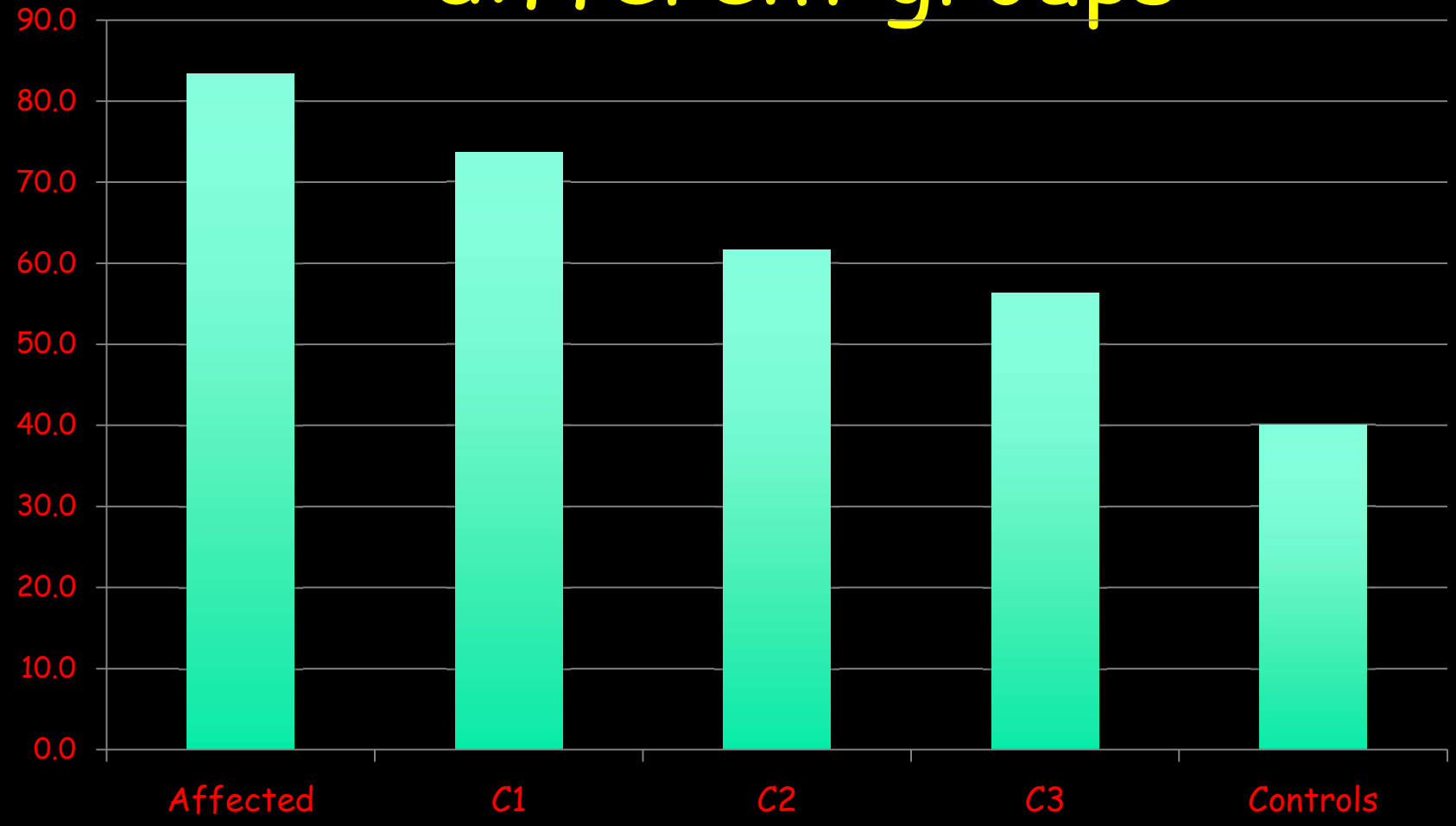
Eight different haplotypes

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



Myositis risk haplotype

% dogs with risk haplotypes in different groups



C1= healthy with a 1st degree affected relative
C2= healthy with a 2nd degree affected relative
C3= healthy with a 3rd degree affected relative

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DLA haplotypes 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 for 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	02101	059v	0.6	Only found in vizslas from USA

SLO = Symmetrical Lupoid Onychodystrophy

Other genetic markers for myositis

Expect to find several groups of genes:

- common to several different autoimmune diseases
- specific for this disease
- specific for certain breeds

An aside: what is a SNP?

-> Single nucleotide polymorphism

DNA has four bases: C, G, T, A

Different people (or dogs) have different bases at particular positions in the genome

The positions that are variable are called SNPs

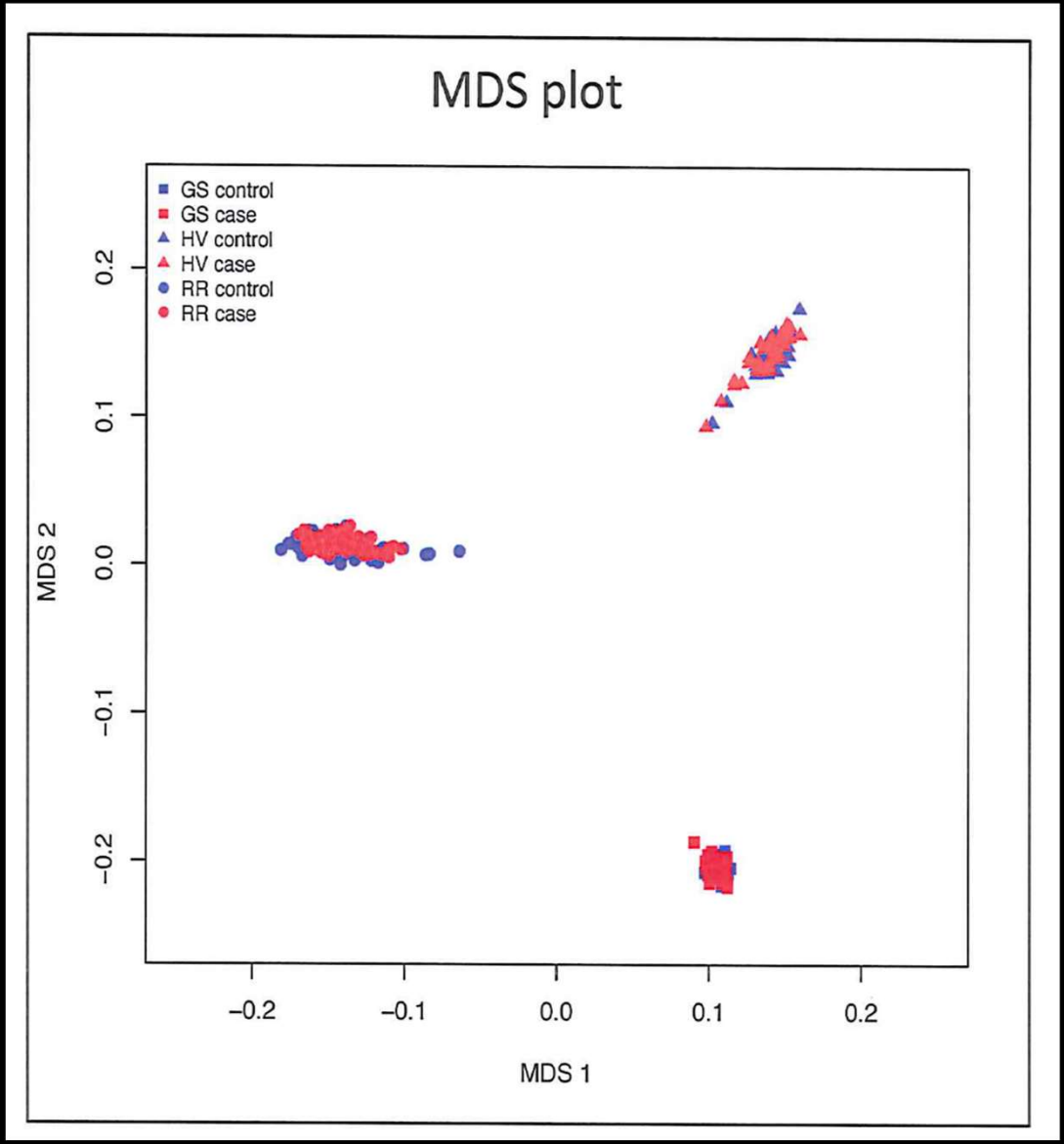
Genome wide association studies (GWAS)

Many SNPs identified in dog genome

Technology developed to screen multiple SNPs: "arrays"

170,000 SNPs evenly spaced throughout the genome

Rhodesian Ridgeback



Hovawart

Gordon Setter

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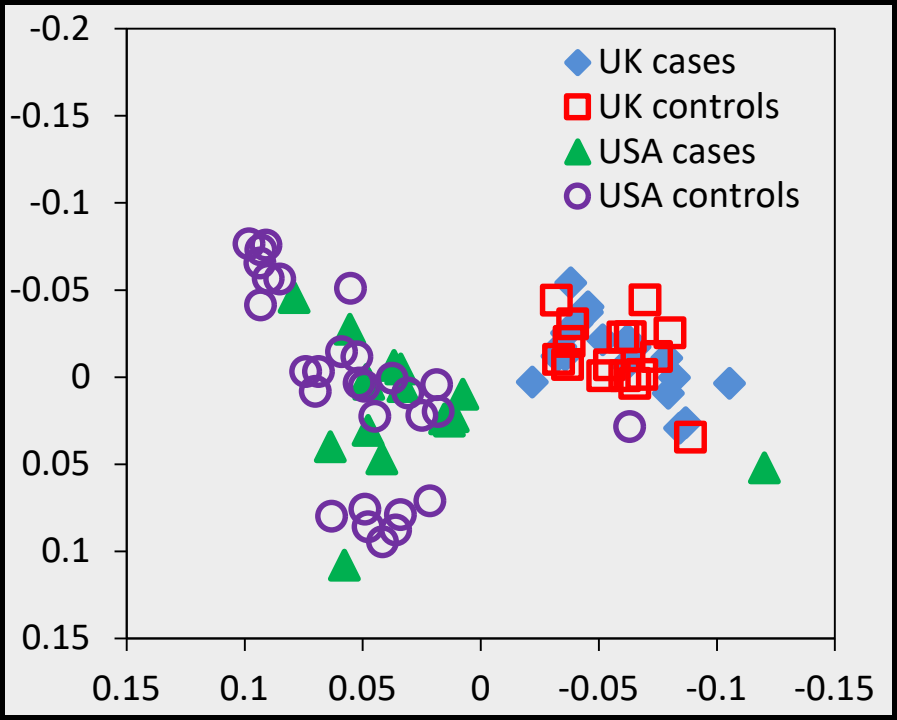
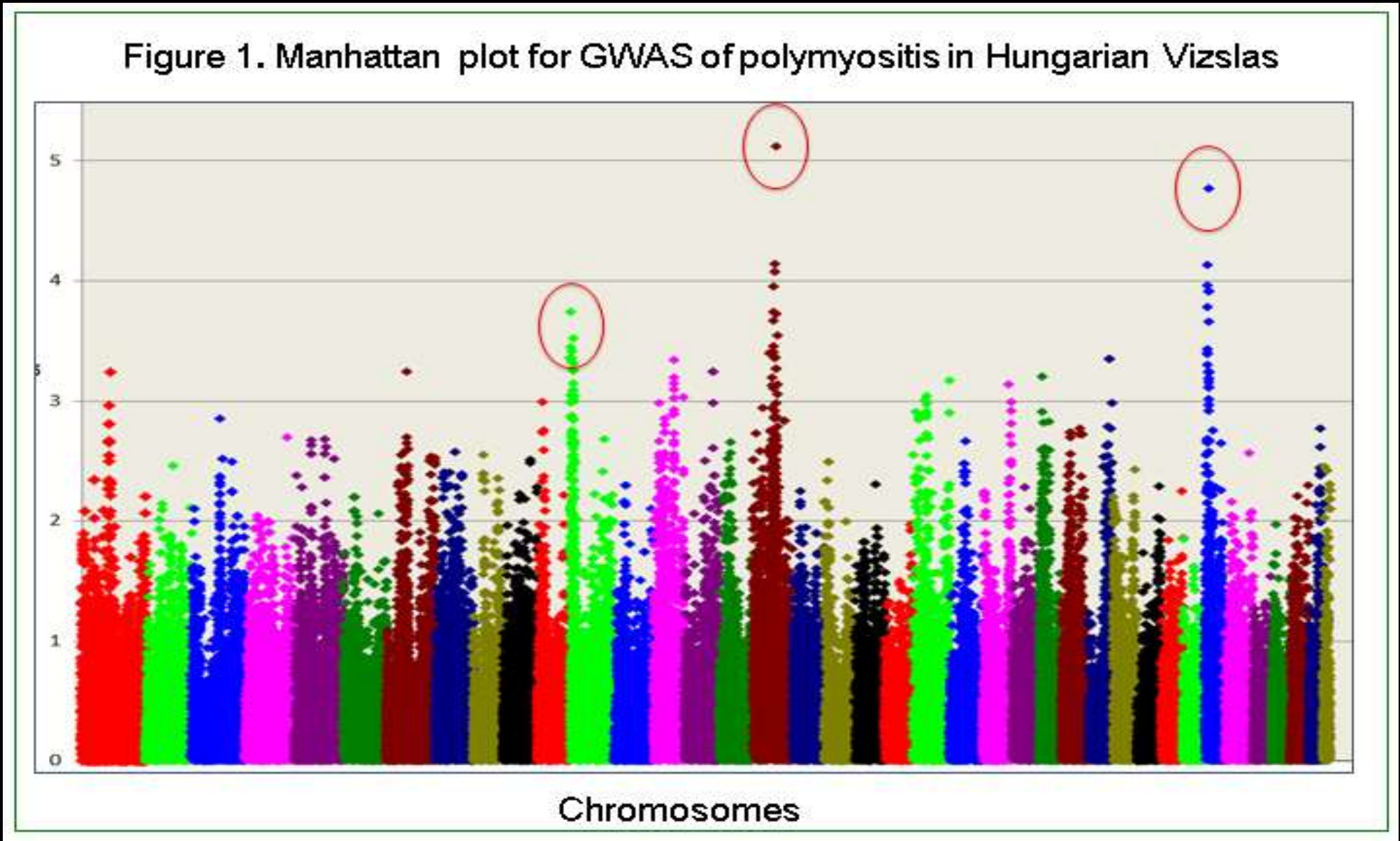
MDS for Dobermann





three regions of suggestive association with the disease ($P<5x10^{-4}$) on canine chromosomes 12, 17 and 33.

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What next?

As science progresses.....

Whole genome sequencing (WGS)

- compare affected dogs with healthy controls
- look for regions that are identical in cases, and different in controls

How many WGS should we do? What might we find?

.....Then need to test in total cohort

Genetic tests for auto-immune diseases?

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Genetic tests for complex diseases

We will need to

- develop genetic tests for each of the genes
- know the relative contribution of each gene

But because we do not yet know the environmental triggers

It is likely you will only get an estimate of the risk of your dog getting the disease

It is unlikely there will ever be definitive YES/NO tests

We all need to understand risk
So what is 10% risk?

If I offered you 10% off a £20 skirt:

you would probably think it was hardly worth having – only £2!

But if I told you that in a litter of 10 puppies, ONE would get an autoimmune disease:

now what do you think about 10%?

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Take home messages

Strong MHC association
with myositis in the Hungarian Vizsla

GWAS has implicated other genes

Next: WGS, and confirmation in all samples

However, 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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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

Should we use MHC data in mate selection?

DLA typing is another tool to use
but NOT the first tool……

Use it as the last tool to choose between two sires:

If bitch is homozygous, try to avoid a sire that is homozygous for the same haplotype

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MHC diversity in breeds

Most breeds have limited MHC diversity

5-7 haplotypes, with 1-2 at high frequency

Changing the MHC profile

i.e. increasing frequency of rarer haplotypes

will NOT increase diversity

[and maybe they are rare for a reason!]

The only way to increase diversity is to introduce other haplotypes (from other lines, or other breeds!!)

Can/should we use MHC data to reduce disease susceptibility?

Dobermann MHC haplotypes

	DRB1	DQA1	DQB1	Freq	Disease
1	00601	00401	01303	71.2	Chronic inflammatory hepatitis
2	01201	00101	00201	13.9	Hypothyroid disease
3	00201	00901	00101	5.3	(Diabetes)
4	00601	005011	00701	4.1	(IMHA)
5	01501	00901	00101	3.8	