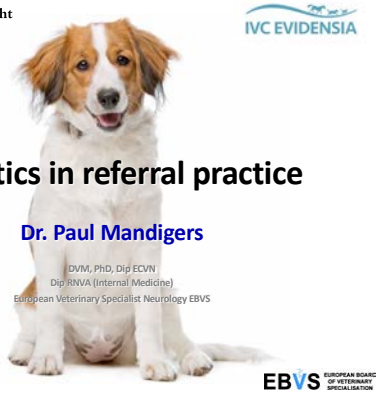
Universiteit Utrecht

IVC EVIDENSIA



Genetics in referral practice

Dr. Paul Mandigers

DVM, PhD, Dip ECVN
Dip RNVA (Internal Medicine)
European Veterinary Specialist Neurology EBVS

EBVS EUROPEAN BOARD OF VETERINARY SPECIALISATION

1

Who am I?

- Veterinary specialist in Neurology (and internal medicine)
- Clinician & researcher
- Teacher

I am not!

- A geneticist

Employment

- Evidensia referral hospitals The Netherlands
- Expertise Centre Genetics Faculty of Veterinary Medicine, Utrecht University

2

What do we do at ECGG?

- We help breeders with direct advise
- Screen breed populations
- Investigate diseases
- Identify mutations
- Develop software to improve sustainable breeding (fit2breed)
- Etc

Dr. Hille Fieten & Dr. Peter Leegwater

Our network: USA, Finland, UK, Swiss, Germany etc

3

Several projects

- Myelopathies
- Polymyositis
- Gastric carcinoma's
- Chiari Malformation / Syringomyelia
- Epilepsy
- Paroxysmal dyskinesia's
- Polyneuropathy's
- And many others,…

4

What are my topics to be discussed

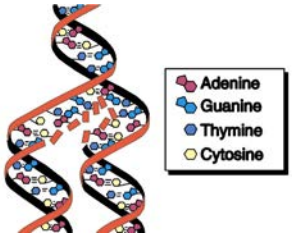
- Basic DNA knowledge
- When is it possible genetic?
- How to approach it

And next,……

5

Basic DNA knowledge

Deoxy-ribo-Nucleic Acid = DNA



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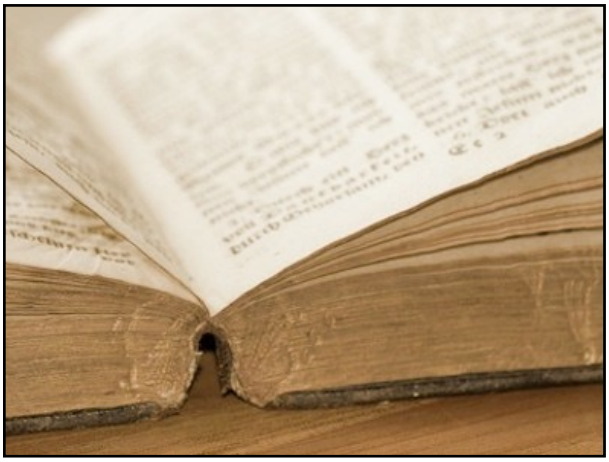

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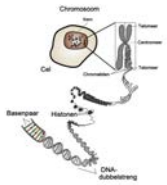
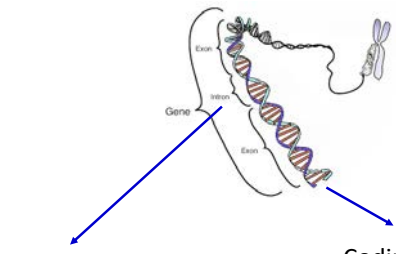
DNA

- The majority is nucleus DNA



- A minority is mitochondrial DNA that you only get from your mother

9



10

A book?

- Up to 98,5 to 99% is non coding DNA (junk DNA)
- Only 1 to 1.5% is coding DNA (the genes)

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DNA

- Contains for base pairs cytosine (C), guanine (G), adenine (A) or thymine (T)

RNA

- Made up with four base pairs guanine (G), uracil (U), adenine (A), and cytosine (C)
- Three base pairs form a codon which translate to a amino acid

12

Non coding DNA

In which we can find microsatellites:

- Single Sequence Repeats (SSR) or repeats.
- > 150 basepairs (varies)
- For example: CACACACACA etc
- Are ''fixed' in the genome
- Occur infrequently in the genome
- Are unique for an individuals and related individuals (family) but vary between non-related individuals (polymorphic)

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Non coding DNA

Microsatellites:

- Often used as markers
  - for instance parental control
  - parental research
  - forensic research, etc
- Also used in linkage analysis
- In cancer diagnostics

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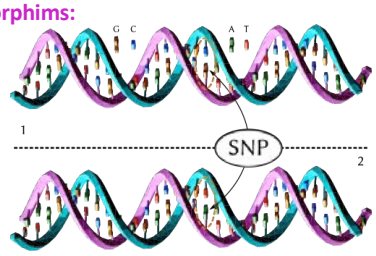
Non coding and coding DNA

In which we can find SNP's or Single Nucleotide Polymorphims:



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SNP's

Non-coding and coding DNA

- Scattered over all chromosomes there are loads of SNP's
- Specific piece of (non-)coding DNA with one base pair that is changed
- F.i.: AAGC**C**TA als AAGC**T**TA

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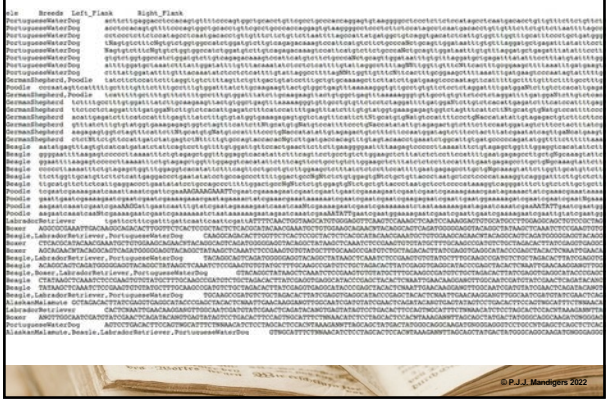
http://www.broadinstitute.org/files/shared/mammals/dog/snp/snp_lists/chr1.dog_snps.txt



17

Image courtesy of Illumina Inc.

SNP chip or microarray

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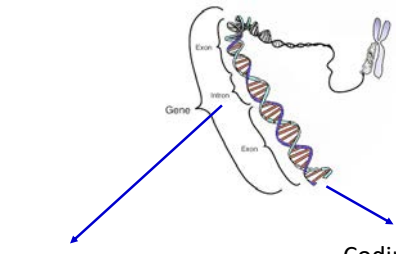
SNP's

Non-coding and coding DNA

- Up to 50.000 SNP's genetic variation & genomic selection
- Starting with 250.000 SNP's genetic research (GWAS)
- In non coding DNA of no consequence (?)
- In a gene: can be of unimportant
  : can be of consequence

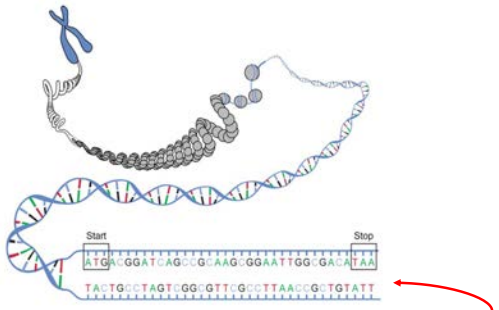
19



Non coding DNA

Coding DNA

20

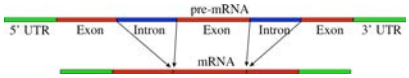


sequence

21

How does it work?

- **Coding DNA** → transcription → pre-mRNA
- pre-mRNA — RNA-processing, splicing, RNA-editing of alternative splicing → **mRNA**
- mRNA— translation → **protein**



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Mutations?

- Substitution
- Insertion
- Deletions

23

Mutations?

- Substitution

24

Mutations?

- Insertion

C A C G A T T C G A T G G A C G T…

C A C G A T T C G A C G A T G G A C …

25

Mutations?

- Deletions

C A C G A T T C G A T G G A C G T…

. C A C G A T A T G G A C …

26

When do we need to think of a hereditary disease?

- Specifically that breed
- Same age group
- Same clinical presentation
- Same pathology
- Familial presentation
- When inbred higher frequency
- A DNA mutation that leads to ….

(Patterson et al., JSAP 1989)

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What kind of research is possible?

a.o.

- Candidate gene approach
- Linkage analysis
- GWAS (Genome Wide Association Study)
- Whole genomic sequencing

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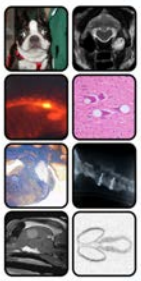
University of Glasgow



L-2-Hydroxyglutaric Aciduria: Characterisation of the molecular defect in a spontaneous canine model.

Jacques Penderis
BVSc MVM PhD CertVR DipECVN MRCVS
European and RCVS recognised specialist in Veterinary Neurology

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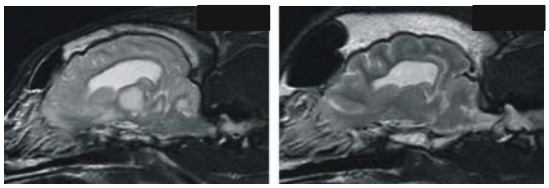
Staffordshire bull terriers

- Same breed
- All young dogs
- Presented with ataxia / epilepsy / muscle stiffness → generalised neurological disorder
- Normal routine clinical chemistry / haematology etc n.a.
- MRI:

31



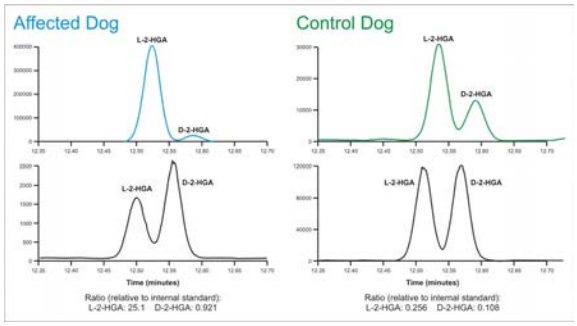
patient control

32

Staffordshire bull terriers

- Metabolic?
- Normal clinical chemistry hence next step is → organic acid analysis

33



34

This enabled genetic research

- The whole genome of both human and dog is 'known'
- The gene involved in degradation of L2HGA is known.
- Hence → candidate gene approach

35

Candidate Gene Analysis of Syntenic Region of Dog Genome

Markers typed within the syntenic region of the dog genome and PCR primers designed to amplify these regions:

Marker Name	Microsatellite marker type	Chromosome 8 start position	F Primer	R Primer
HGA-1	Tetra-nucleotide: CTTT	29 308 249	TgAgACTCCAgggATATgAACA	TgAgACTCCAgggATATgAACA
HGA-2	Tetra-nucleotide: CTTT and AG	29 390 165	CTgCCACAgTgCCTTCAAT	CTgCCACAgTgCCTTCAAT
HGA-3	Tetra-nucleotide: GAAA	29 458 543	CCAgggCCTgATAgAATCAA	CCAgggCCTgATAgAATCAA
HGA-4	TC + TA	29 641 685	TATgTgCAgCCTTggCATAg	TATgTgCAgCCTTggCATAg

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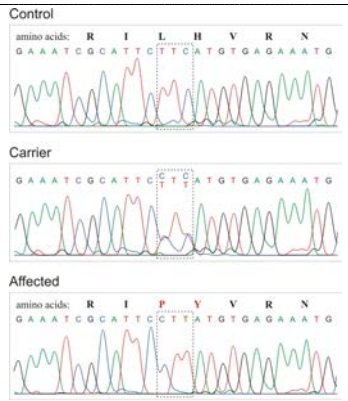
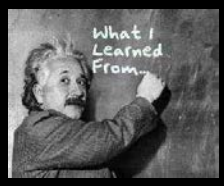
Exon 10:



37



Take home message!

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What to do when you suspect a genetic origin?

- Identify what you are observing
- If possible get proper pathology

→ This is **fenotyping**. *The better you can do it, the greater the change for success*

- If the genes involved are known: *it is possible to do a candidate gene approach*
- If not a different approach is needed

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If it is in one family

Linkage analysis

- Linkage analysis is a genetic method that searches for chromosomal segments that cosegregate with the ailment phenotype through families

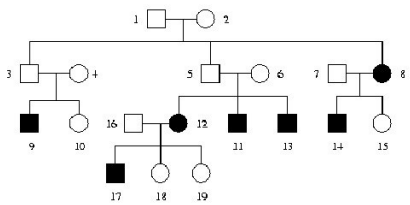
- LOD score (logarithm (base 10) of odds)
- The LOD score compares the likelihood of obtaining the test data if the two loci are indeed linked, to the likelihood of observing the same data purely by chance

40

If it is in one family

Linkage analysis

- Microsatellites (limited use)
- GWAS



41

Next!

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Juvenile paroxysmal dyskinesia in Markiesje dogs

43

Human Genetics
https://doi.org/10.1007/s00439-021-02271-6

ORIGINAL INVESTIGATION

A knockout mutation associated with juvenile paroxysmal dyskinesia in Markiesje dogs indicates *SOD1* pleiotropy

P. J. J. Mandigers[1] · F. G. Van Steenbeek[1] · W. Bergmann[2] · M. Vos-Loohuis[1] · P. A. Leegwater[1]

Received: 3 December 2020 / Accepted: 23 February 2021

Abstract
A juvenile form of paroxysmal dyskinesia segregated in the Markiesje dog breed. Affected pups exhibited clinical signs of a severe tetraparesis, dystonia, cramping and falling over when trying to walk. In most cases, the presentation deteriorated within weeks and elective euthanasia was performed. Pedigree analysis indicated autosomal recessive inheritance. Genome-wide association and homozygosity mapping of 5 affected dogs from 3 litters identified the associated locus on chromosome 31 in the region of *SOD1*. The DNA sequence analysis of *SOD1* showed that the patients were homozygous for a frameshift mutation in the fourth codon. None of the other analyzed dogs of the breed was homozygous for the mutation, indicating full penetrance of the genetic defect. Mutations in *SOD1* are known to cause recessive degenerative myelopathy in middle-aged dogs with low penetrance and dominant amyotrophic lateral sclerosis in humans with variable age of onset. Our findings are similar to recent observations in human patients that a loss of function mutation in *SOD1* leads to a juvenile neurologic disease distinct from amyotrophic lateral sclerosis.

44

Paroxysmal Dyskinesia

45

Courtesy Jacques Penderis

46

Courtesy Dennis O'Brein

47

48

Presentation:

- A total of seven litters with 14 affected pups (males and females) out of 36 pups
- All the same breed, same clinical presentation, ‘similar’ pathology
- 1 out of 4
- Parents not affected
- Most likely genetic →
- Autosomal recessive disorder

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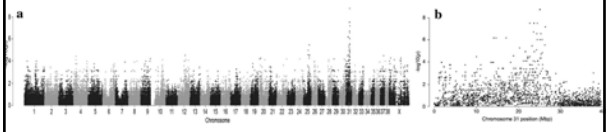
What we did:

- The pathology didn’t help us a lot. It was minimal.
- We identified affected (fenotyped) and non affected dogs.
- Collected DNA samples from EDTA bloodsamples
- Got funding!
- Started with a GWAS

50

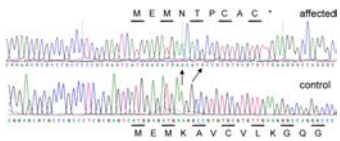


51

Hence,…

- A clear significant log value on chromosome 31 (SOD1 is over there)
- We sequenced this region

52



DNA sequence of the translation start region of exon 1 of SOD1 in Markiesje dogs with and without paroxysmal dyskinesia.

In the affected dog, the first of two G-residues is replaced by the trinucleotide CAC. The arrows indicate unaltered A- and G-residues.
The mutation leads to a frameshift at the 4th codon of the gene. Then codons are indicated by alternating lines with the encoded

53

Conclusion:

- A frameshift in SOD1 that results in a knockdown of the gene
- Model for ALS in children (translational medicine)
- Disorders solved in this breed!

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Research in Veterinary Science 1993, 54, 118-123

Hereditary necrotising myelopathy in Kooiker dogs

P. J. J. MANDIGERS, *Department of Pathology*, J. J. VAN NES, B. W. KNOL, G. J. UBBINK, *Department of Clinical Sciences of Companion Animals*, E. GRUYS, *Department of Pathology, Faculty of Veterinary Medicine, University of Utrecht, Yalelaan 1, 3508 TD Utrecht, The Netherlands*

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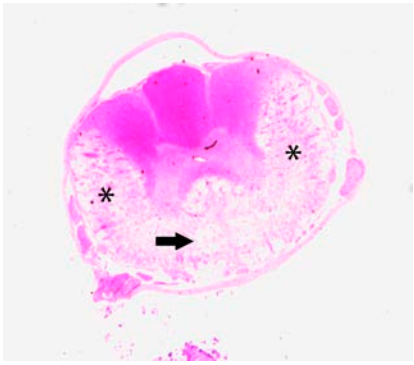

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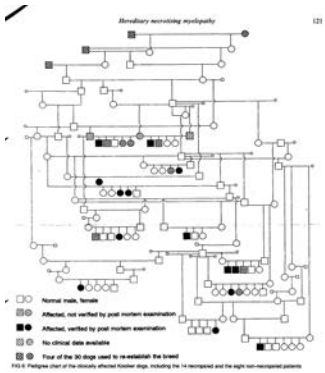

58

HNM

Inheritance:

- Autosomal
- Recessive
- Simple

	A	a
A	AA	Aa
a	Aa	aa

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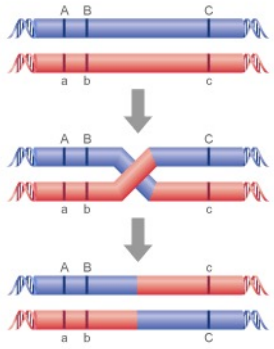
What we did:

- We knew it is genetic
- Collected cases and controls
- A GWAS only revealed a region but we were not able to pinpoint yet the mutation.
- We used a marker close to the mutation not known yet
- But that helped to prevent cases being born

60



Lindblad-Toh et al

61

We continued our research:

- We performed a Whole Genomic Sequence
- So the complete region was examined.
- The mutation is now found and we test for this.
- The mutation causes that the myelin disappears
- It will be published this year.

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www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Canine *NAPEPLD*-associated models of human myelin disorders

K. M. Minor[1], A. Letko[2], D. Becker[2], M. Drögemüller[2], P. J. J. Mandigers[3], S. R. Bellekom[3], P. A. J. Leegwater[3], Q. E. M. Stassen[3], K. Putschbach[4], A. Fischer[4], T. Flegel[5], K. Matiasek[4], K. J. Ekenstedt[6], E. Furrow[7], E. E. Patterson[1], S. R. Platt[7], P. A. Kelly[8], J. P. Cassidy[8], G. D. Shelton[9], K. Lucot[10], D. L. Bannasch[10], H. Martineau[11], C. F. Muir[11], S. L. Priestnall[11], D. Henke[12], A. Oevermann[13], V. Jagannathan[2], J. R. Mickelson[1] & C. Drögemüller[2]

Received: 6 November 2017
Accepted: 20 March 2018
Published online: 11 April 2018

Canine leukoencephalomyelopathy (LEMP) is a juvenile-onset neurodegenerative disorder of the CNS white matter currently described in Rottweiler and Leonberger dogs. Genome-wide association study (GWAS) allowed us to map LEMP in a Leonberger cohort to dog chromosome 18. Subsequent whole genome re-sequencing of a Leonberger case enabled the identification of a single private homozygous non-synonymous missense variant located in the highly conserved metallo-beta-lactamase domain of the *N-acyl phosphatidylethanolamine phospholipase D* (*NAPEPLD*) gene, encoding an enzyme of the endocannabinoid system. We then sequenced this gene in LEMP-affected Rottweilers and identified a different frameshift variant, which is predicted to replace the C-terminal metallo-beta-lactamase domain of the wild type protein. Haplotype analysis of SNP array genotypes revealed that the frameshift variant was present in diverse haplotypes in Rottweilers, and also in Great Danes, indicating an old origin of this second *NAPEPLD* variant. The identification of different *NAPEPLD* variants in dog breeds affected by leukoencephalopathies with heterogeneous pathological features, implicates the NAPEPLD enzyme as important in myelin homeostasis, and suggests a novel candidate gene for myelination disorders in people.

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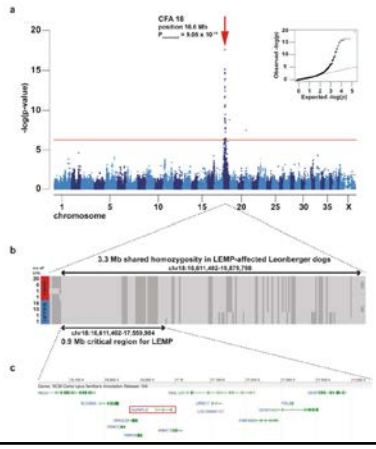

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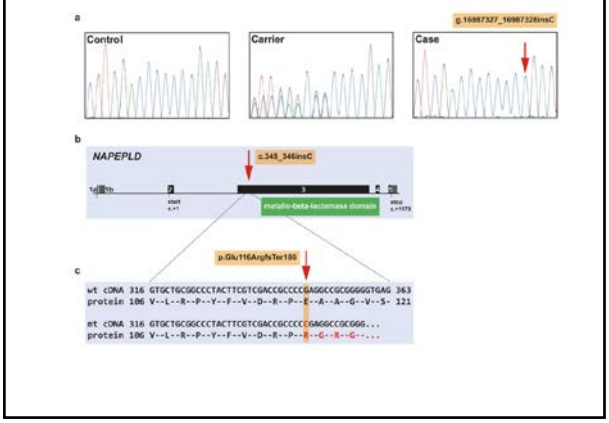

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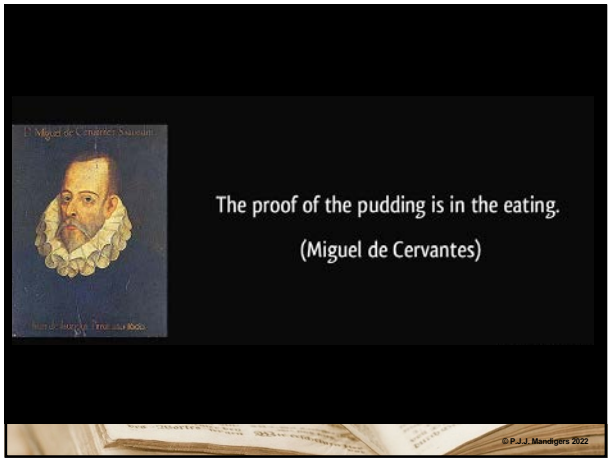

66

When a mutation is found:

- Proof that it causes the disease
- Is it just for this breed?
- And if it occurs in different breeds does it come to expression?

67

Patterson EE, Minor KM, Tchernatynskaia AV, Taylor SM, Shelton GD, Ekenstedt KJ, Mickelson JR.

A canine DNM1 mutation is highly associated with the syndrome of exercise-induced collapse

Nat Genet. 2008 Oct;40(10):1235-9. Epub 2008 Sep 21

68

69

70

Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis

Awano T, Johnson GS, Wade CM, Katz ML, Johnson GC, Taylor JF, Perloski M, Biagi T, Baranowska I, Long S, March PA, Olby NJ, Shelton GD, Khan S, O'Brien DP, Lindblad-Toh K, Coates JR

Proc Natl Acad Sci U S A. 2009 Feb 24;106(8):2794-9

71

72

Genetic research

Genome-wide association analysis reveals a SOD1 mutation in canine degenerative myelopathy that resembles amyotrophic lateral sclerosis

Awano T, Johnson GS, Wade CM, Katz ML, Johnson GC, Taylor JF, Perloski M, Biagi T, Baranowska I, Long S, March PA, Olby NJ, Shelton GD, Khan S, O'Brien DP, Lindblad-Toh K, Coates JR

Proc Natl Acad Sci U S A. 2009 Feb 24;106(8):2794-9

ALL BREEDS

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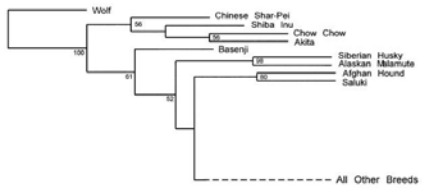
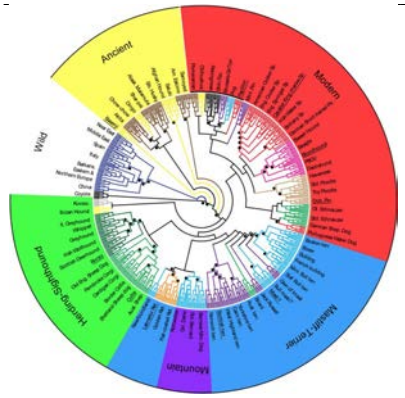
Genetic research



From Parker HG, Genomic analysis of modern dog breeds (2012) mamm Genome 23-19-27

75

Genetic research



From vonHolt et al (2011) A genome-wide perspective of the evolutionary history of Enigmatic wolf-like canids. Genome Research, 21:1294-1305

76

Genetic research

Zeng et al, 2014

Breed distribution of SOD1 allels *previously* associated with canine degeneratieve myelopathy

J. Vet. Internal Medicine

77

Genetic research

Zeng et al, 2014

35.359 bloodsamples analysed

249 histopathology cases

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Degenerative myelopathy (DM)

histopathology

- All affected dogs had DM
- Heterozygotes → Eight dogs (out of 249 = 3%) got DM

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Table 1. Genotypes at *SOD1 c.118* and A allele frequencies for breeds with at least 50 tested members.

Breed	Number Tested	Genotype G/G	G/A	A/A	A Allele Frequency
Wire Fox Terrier	79	1	7	71	0.94
Pembroke Welsh Corgi	3,209	220	898	2,091	0.79
Boxer	3,934	500	1,177	2,257	0.72
Cavalier King Charles Spaniel	73	10	27	36	0.68
Pit Bull Terrier	53	23	6	24	0.51
American Water Spaniel	91	22	46	23	0.51
Australian Shepherd	113	57	20	36	0.41
Collie	151	73	39	39	0.39
Soft Coated Wheaten Terrier	88	45	18	25	0.39
Hovawart	64	31	17	16	0.38
Bernese Mountain Dog	2,413	941	1,112	360	0.38
Chesapeake Bay Retriever	2,344	958	1,034	352	0.37
German Shepherd Dog	6,458	3,155	1,884	1,419	0.37
Tibetan Terrier	69	32	24	13	0.36
Kerry Blue Terrier	558	254	223	81	0.34
Czechoslovakian Wolfdog	52	24	21	7	0.34
Cardigan Welsh Corgi	544	271	194	79	0.32
Pug	382	202	113	67	0.32
Jack Russell Terrier	60	36	10	14	0.32
Bloodhound	264	125	117	22	0.30
Canaan Dog	169	87	67	15	0.29
Rhodesian Ridgeback	2,645	1,381	1,023	241	0.28
Kuvasz	75	46	19	10	0.26
Welsh Terrier	72	41	25	6	0.26
Komondor	55	32	22	1	0.22
Shetland Sheepdog	58	41	10	7	0.21
Tamaskan (Aslu Tamaskan)	59	40	17	2	0.18
Puli	123	83	29	7	0.17
Borzoi	787	548	209	30	0.17
English Springer Spaniel	127	97	17	13	0.17
Border Collie	80	63	7	10	0.17
French Bulldog	87	64	18	5	0.16
Irish Setter	57	42	12	3	0.16
Shiloh Shepherd	221	161	53	7	0.15
Great Pyrenees	85	68	10	7	0.14
Saint Bernard	78	60	15	3	0.13
Chinese Crested	53	40	13	0	0.12
Staffordshire Bull Terrier	52	46	1	5	0.11
Mastiff (English Mastiff)	114	93	19	2	0.10
Norwich Terrier	74	60	14	0	0.09
Australian Cattle Dog	61	53	5	3	0.09
Coton de Tulear	110	94	16	0	0.07
Labrador Retriever	475	433	19	23	0.07
Nova Scotia Duck Tolling Ret.	59	52	6	1	0.07
Poodle-Standard	533	468	60	5	0.07
Beagle	57	52	3	2	0.06
Belgian Malinois	101	92	6	3	0.06
Teriorfield Terrier	66	59	7	0	0.05
Siberian Husky	97	92	3	2	0.04
Dalmatian	180	172	4	4	0.03
Golden Retriever	334	322	2	10	0.03
Rottweiler	76	73	2	1	0.03
Doberman Pinscher	55	54	0	1	0.02
Alaskan Malamute	61	60	0	1	0.02
Newfoundland	62	61	0	1	0.02
Rat Terrier	63	62	1	0	0.01

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Breed	Number Tested	Genotype G/G	G/A	A/A	A Allele Frequency
Wire Fox Terrier	79	1	7	71	0.94
Pembroke Welsh Corgi	3,209	220	898	2,091	0.79
Boxer	3,934	500	1,177	2,257	0.72
Cavalier King Charles Spaniel	73	10	27	36	0.68
Pit Bull Terrier	53	23	6	24	0.51
American Water Spaniel	91	22	46	23	0.51
Australian Shepherd	113	57	20	36	0.41
Collie	151	73	39	39	0.39
Soft Coated Wheaten Terrier	88	45	18	25	0.39
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PNAS PLUS

Variants within the SP110 nuclear body protein modify risk of canine degenerative myelopathy

Emma L. Ivansson[a,b,1,2], Kate Megquier[a,b], Sergey V. Kozyrev[a], Eva Murén[a], Izabella Baranowska Körberg[c,d], Ross Swofford[e], Michele Koltookian[e], Noriko Tonomura[b,d], Rong Zeng[e], Ana L. Kolicheski[a], Liz Hansen[a], Martin L. Katz[f], Gayle C. Johnson[a], Gary S. Johnson[a], Joan R. Coates[g], and Kerstin Lindblad-Toh[a,b,1]

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Edited by Stephen T. Warren, Emory University School of Medicine, Atlanta, GA, and approved April 15, 2016 (received for review January 7, 2016)

Canine degenerative myelopathy (DM) is a naturally occurring neurodegenerative disease with similarities to some forms of amyotrophic lateral sclerosis (ALS). Most dogs that develop DM are homozygous for a common superoxide dismutase 1 gene (*SOD1*) mutation. However, not all dogs homozygous for this mutation develop disease. We performed a genome-wide association analysis in the Pembroke Welsh Corgi (PWC) breed comparing DM-affected and -unaffected dogs homozygous for the *SOD1* mutation. The analysis revealed a modifier locus on canine chromosome 25. A haplotype within the SP110 nuclear body protein (SP110) was present in 40% of affected compared with 4% of unaffected dogs ($P = 1.5 \times 10^{-9}$), and was associated with increased probability of developing DM ($P = 4.8 \times 10^{-4}$) and earlier onset of disease ($P = 1.7 \times 10^{-5}$). SP110 is a nuclear body protein involved in the regulation of gene transcription. Our findings suggest that variations in SP110-mediated gene transcription may underlie, at least in part, the variability in risk for developing DM among PWCs that are homozygous for the disease-related *SOD1* mutation. Further studies are warranted to clarify the effect of this modifier across dog breeds.

degenerative myelopathy | amyotrophic lateral sclerosis | ALS | SOD1 | SP110

Amyotrophic lateral sclerosis (ALS) is the most common

several clinical subtypes with variable phenotypic presentation and prognosis.

Over 20 y ago, a mutation in the superoxide dismutase 1 gene (*SOD1*) was the first genetic risk factor to be identified (4). To date, more than 160 *SOD1* mutations involving all five exons have been identified in patients with ALS (alsod.iop.kcl.ac.uk) (5). *SOD1* has been followed by a growing list of ALS-associated genes (6–8), including an intronic repeat expansion in chromosome 9 open reading frame 72 (*C9ORF72*) present in patients

Significance

Degenerative myelopathy (DM) is a canine disease very similar to amyotrophic lateral sclerosis (ALS) in humans. We previously showed that DM is a promising model for ALS, because genome-wide association identified a mutation in superoxide dismutase 1 gene (*SOD1*), a known ALS gene. This mutation found in many dog breeds increases the risk of DM, and the pathological findings and clinical progression of the two diseases are similar. In this study, we identify a modifier gene, SP110 nuclear body protein (SP110), which strongly affects overall disease risk and age of onset in Pembroke Welsh Corgis at risk for DM. Dissecting the complex genetics of this disease in a model organism may lead to new insights about risk and progression in both canine

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Degenerative myelopathy

Welsh Corgi Pembroke

- A variant of a transcription gene which means:
- Not all dogs will get affected

or

- Get affected at the same age

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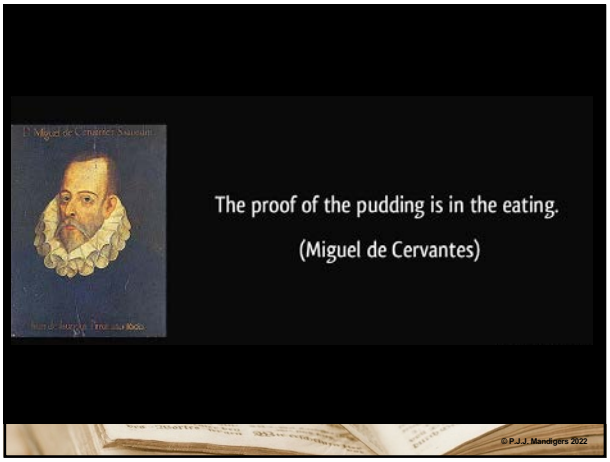

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Universiteit Utrecht

IVC EVIDENSIA

Epilepsy

Dr. Paul Mandigers

Clinical Associate Professor
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European Veterinary Specialist Neurology EBVS

University Utrecht
Department of clinical Sciences of Companion Animals
Neurology

EBVS EUROPEAN BOARD OF VETERINARY SPECIALISATION

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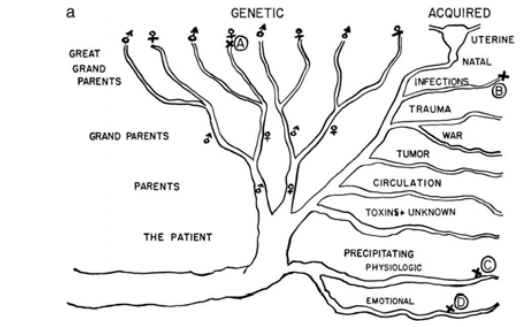

From Shorvon, epilepsy and behavior, 2014

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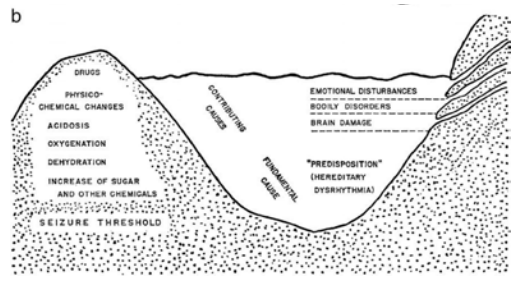

Shorvon, epilepsy and behavior, 2014

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Hülsmeyer et al. BMC Veterinary Research (2015) 11:175
DOI 10.1186/s12917-015-0463-0

BMC Veterinary Research

CORRESPONDENCE Open Access

International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs

Velia-Isabel Hülsmeyer[1*], Andrea Fischer[1], Paul J.J. Mandigers[2], Luisa DeRisio[3], Mette Berendt[4], Clare Rusbridge[5,6], Sofie F.M. Bhatti[7], Akos Pakozdy[8], Edward E. Patterson[9], Simon Platt[10], Rowena M.A. Packer[11] and Holger A. Volk[11]

Abstract

Canine idiopathic epilepsy is a common neurological disease affecting both purebred and crossbred dogs. Various breed-specific cohort, epidemiological and genetic studies have been conducted to date, which all improved our knowledge and general understanding of canine idiopathic epilepsy, and in particular our knowledge of those breeds studied. However, these studies also frequently revealed differences between the investigated breeds with respect to clinical features, inheritance and prevalence rates. Awareness and observation of breed-specific differences is important for successful management of the dog with epilepsy in everyday clinical practice and furthermore may promote canine epilepsy research. The following manuscript reviews the evidence available for breeds which have been identified as being predisposed to idiopathic epilepsy with a proven or suspected genetic background, and highlights different breed specific clinical features (e.g. age at onset, sex, seizure type), treatment response, prevalence rates and proposed inheritance reported in the literature. In addition, certain breed-specific diseases that may act as potential differentials for idiopathic epilepsy are highlighted.

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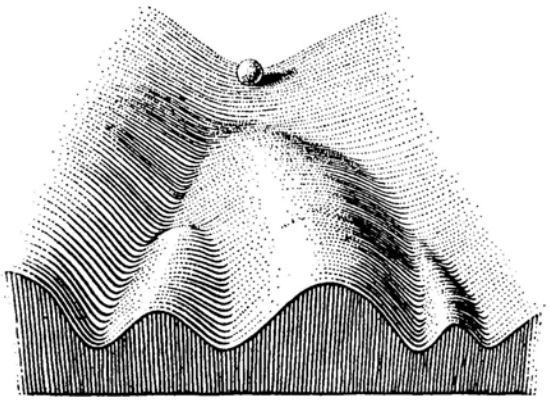

Waddinton's landscape

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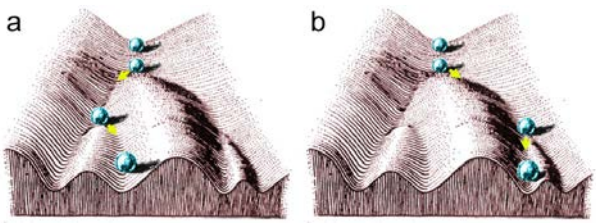

Waddinton's landscape

90

Breed specific:
(hereditary)

- All **shepherds** such as German, Belgian shepherd, Border collie, etc, etc
- All **molossoid** breeds such as St. Bernard, Great dane, Boxer, etc, etc)
- All **hunting dogs** such as German pointer, English springer, Golden Retriever, Labrador retriever, Fauve E.B, etc, etc

- Chihuahua and French bulldog

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Table 1 Depicting breed-specific data regarding age of seizure onset

Breed	Age at seizure onset	Reference
Australian Shepherd	2.5 years (median)	Weissl et al. 2012 [3]
Belgian Shepherd	3.3 years (mean)	Berendt et al. 2008 [23]
	3.3 years (mean)	Seppala et al. 2012 [34]
Bernese Mountain dog	26.5 months (mean)	Kathmann et al. 1999 [45]
Border Collie	2.5 years (median)	Hülsmeyer et al. 2010 [8]
Border Terrier	3.2 years (mean)	Kloene et al. 2008 [26]
Dalmatian	2.9 years (median), 3.2 years (mean)	Licht et al. 2002 [65]
English Springer Spaniel	3 years (median)	Patterson et al. 2005 [74]
Finnish Spitz	3 years (median)	Viitmaa et al. 2013 [82]
Golden Retriever	27.5 months (mean)	Srenk et al. 1994 [84]
	24.9 months (mean)	Lengweiler&Jaggy 1999 [86]
Hungarian (Magyar) Vizsla	3 years (median)	Patterson et al. 2003 [67]
Irish Wolfhound	by the age of 3 years in 73 % of dogs	Casal et al. 2006 [24]
Italian Spinone	38 months (mean)	De Risio et al. 2015 [93]
Labrador Retriever	30.6 months (mean)	Jaggy et al. 1998 [95]
	34 months for males and 28 months for females (mean)	Heynold et al. 1997 [94]
	by the age of 4 years in 76 % of dogs	Berendt et al. 2002 [26]
Lagotto Romgancio	6.3 weeks (mean)	Jokinen et al. 2007 [105]
Petit Basset Griffon Vendeen	2 years (median)	Gullov et al. 2011 [25]
Shetland Sheepdog	predominantly between 1 and 1.5 years	Morita et al. 2002 [109]
Standard Poodle	3.7 years (median)	Licht et al. 2007 [113]
	2.4 years (median), 2.8 years (mean)	Licht et al. 2002 [65]

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Paul J.J. Mandigers

Het voorkomen van epilepsie bij de Nederlandse hondenrassen.

Tijdschrift voor Diergeneeskunde, 2017; 142 (2); 28-31

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Tabel 1 Voor de negen rassen aangegeven de tijdvakken, het aantal honden met vermoedelijke epilepsie, de totale populatiegrootte en de incidentie in percentage. Wat opvalt zijn de grote verschillen in incidentie per ras. Bij de Drentse patrijshond staan twee tijdvakken vermeld in verband met een gewijzigde methode van onderzoek na 2005.

	Hollandse Smoushond	Markiesje	Wetterhoun	Stabij	Hollandse herder			Schapendoes	Drentse patrijs	Drentse patrijs	Kooikerhondje	Saarloos wolfhond
					Korthaar	Langhaar	Ruwhaar					
Tijdvak	1995-2015 (20 jaar)	1997-2003 (6 jaar)	1990-2013 (23 jaar)	1990-2013 (23 jaar)	2002-2014 (12 jaar)			1990-2015 (25 jaar)	1995-2005 (10 jaar)	2006-2011 (5 jaar)	2000-2015 (15 jaar)	1980-2013 (33 jaar)
Aantal honden met Epilepsie	34	6	1	92	5	2	1	38	86	51	45	37
Totale populatie	2069	2400	2099	6183	2462	906	516	20763	5071	2344	3000	1770
Incidentie in percentage	0.77%	0.25%	0.05%	1.49%	0.2%	0.22%	0.19%	0.18%	1.7%	2.18%	1.5%	2.1%

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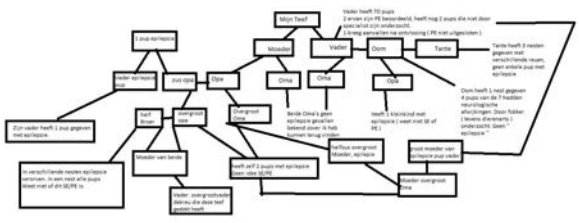
Familial



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Hereditary?

- In many breeds we will find a ***simple autosomal recessive hereditary***
- Boxers, Labrador retrievers, Golden retrievers, Tervueren, Springer spaniëls, Viszla's, Bernese mountian dogs,…etc

- WHY?

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WHY?

Most important reason:

- Dog breeds are highly inbred populations
- We simply can not conclude otherwise

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Why is genetic research so difficult in epilepsy?

Most important reason:

- We miss cases

and

- We included cases that are not cases

98

Genetic epilepsy

What's known in dogs?

99

Lagotto Romagnolo

Belgian Shepherd

Rhodesian Ridgeback

100

What did we discuss so far?

- Basic DNA knowledge
- When is it possible genetic?
- How to approach it

And next,……

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http://www.broadinstitute.org/files/shared/mammals/dog/snp/snp_lists/chr1.dog_snps.txt

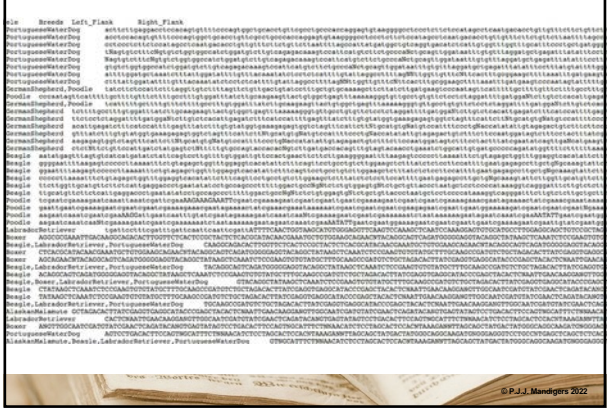

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Image courtesy of Illumina Inc.

SNP chip or microarray

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Genotyping using a SNP chip

SNP's:

- Chips can go from 10.000 to 700.000 SNP's
- Up to 50.000 SNP's genetic variation & genomic selection
- Starting with 250.000 SNP's genetic research (GWAS)

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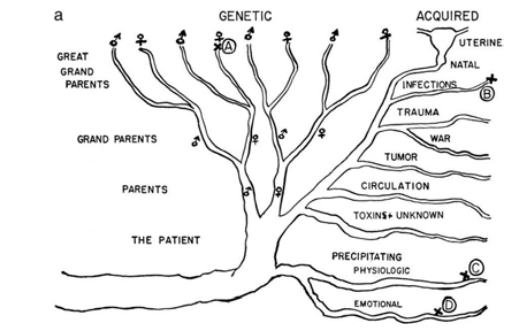

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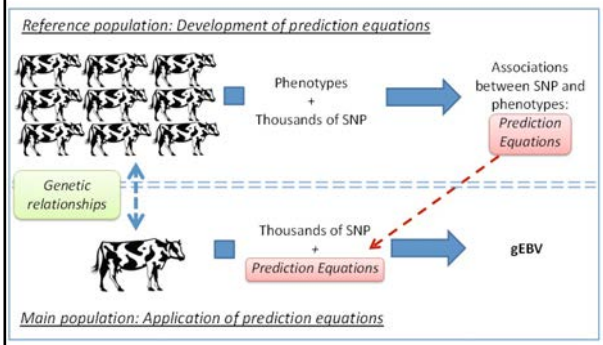

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How can you do use this knowledge as an individual breeder of club?

- Several mutations are known → prevent diseases
- We have constant inbreeding → how to get away from it?

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Genotyping using a SNP chip

F.i. wisdom panel:

- Genotyping (100.000 to 200.000 SNP's)
- Compare within the breed and other dogs/breeds: → genetic variation

- Test for all mutations known
- Test for several traits (coat colours etc)

- Look-alikes: is this dog interesting?

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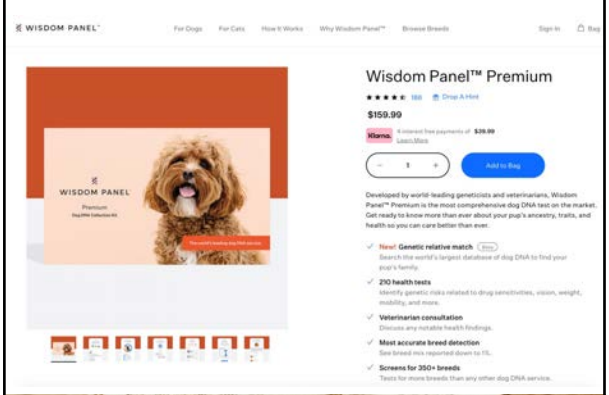

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Wisdom panel a.o.

Handy test – 'want-to-have'

- Genotyping (100.000 to 200.000 SNP's)
- What breed is your dog?
- Compare within the breed
- Compare with other dogs/breeds – genetic variation
- Test for all mutations known
- Test for several traits (coat colours etc)

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But be aware!!

- 20.000 genes
- A variety of variants & mutations
- Several occur is different breeds
- Many are breed specific

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What did we discuss?

- How is it done!
- How can we use it → Dr. Hille Fieten
- Can we use it? → Mr. Jur Deckers

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When you think of a genetic disorder:

- Phenotype!
- Store DNA (cheek mucosa sample or EDTA sample) of the affected dog (and parents / siblings)
- Is somebody busy with it contact them OR contact me/us

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