Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Welfare from a breeding point of view: WFFS & other hereditary diseases in sport horses

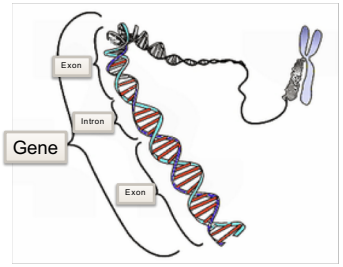
Sofia Mikko
Dept of Animal Breeding and Genetics, Swedish University of Agricultural Sciences
WBFSH Annual meeting, Budapest, 2 November 2018

Traditional breeding goes genomic

- **Breeders choice**
  - Visual inspection by breeder or judge
  - Breeder experience
- **Breeding values**
  - Objective measures
  - Multifactorial traits
- **Molecular genetics**
  - Monogenetic traits
  - Mutations result in altered/nonfunctional protein
- **Genomics**
  - Multigenic/multifactorial traits
  - Find the biological function behind selected traits
- **Genetic & genomic selection**
  - Marker assisted selection
  - Genomic selection

DNA-structure

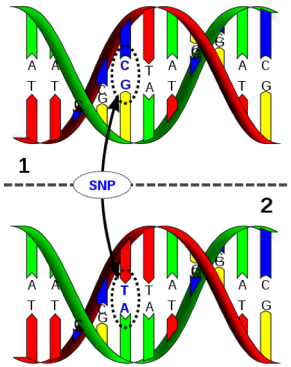
- Chromosomes
- Double stranded DNA
- Genes
- Exons & introns



Mutations

Random mitakes during DNA-duplication

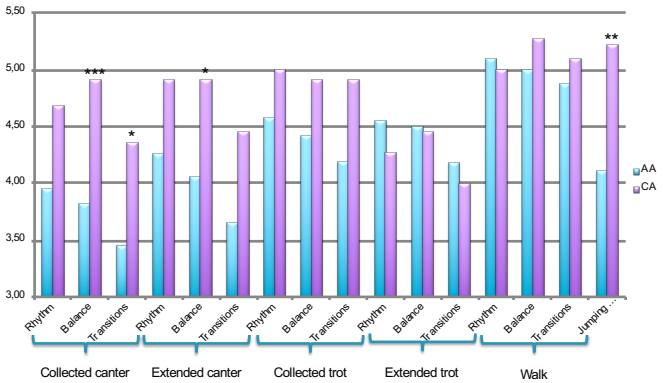
Mutation = “Single Nucleotide Polymorphism” (SNP)



DMRT3 homozygous A/A standardbred

DMRT3 heterozygous C/A standardbred

Gait scores in AA or CA Standardbreds



Jäderkvist et al 2015

Myostatin in Thoroughbreds

EQUINOME

Cracking the code:
The Speed Gene Revealed

C:C C:T T:T

Dr. Emmeline Hill
Equinome Ltd., NovaUCD, Belfield Innovation Park, Belfield, Dublin 4
Email: Emmeline.Hill@equinome.com

Myostatin in thoroughbreds

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"Loss-of-function" mutation

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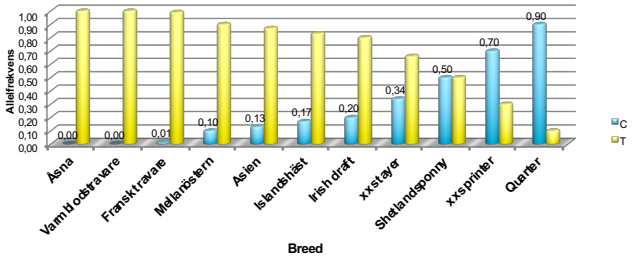
More and larger muscle fibres

Hill *et al.* 2010, Mackowski *et al.* 2010

Myostatin in other breeds



American Standardbreds are fixed for the wild type allele (T).
Allele freq of the "sprinter mutation" (C) in French Trotters is 1%, which means that 2% of them are carriers of the "sprinter mutation".

Bower et al. Nature Genetics, 2012

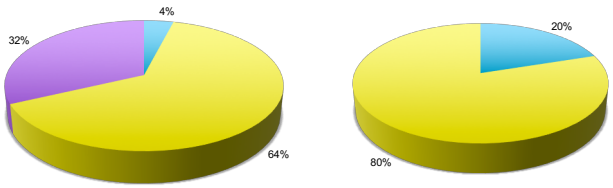
How common is a mutation?

Genotype frequency

At individual level in the population

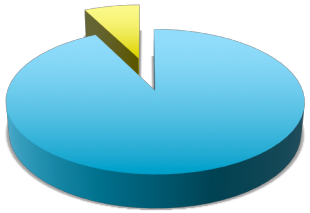
Allele frequency (=mutation freq)

At gene level in the population

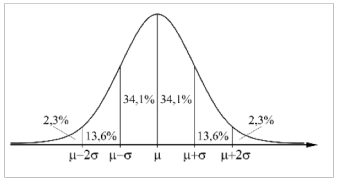


Carrier frequencies

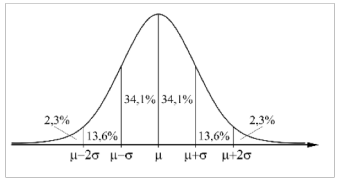
Calculate from a random sample of the population

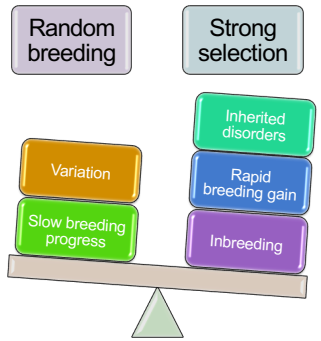


When breeding and selection goes wrong



When breeding and selection goes wrong





Polysaccharide Storage Myopathy – PSSM, Type 1 & Type 2

Type 1:

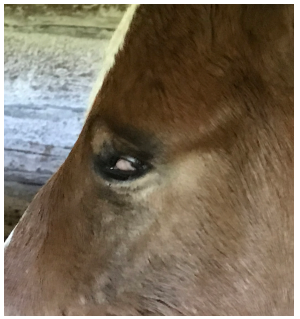
- Increased muscle glycogen conc and abnormal polysaccharide accumulation in skeletal muscle
- Glycogen syntase (GS) encoded by the gene GYS1, autosomal dominant or codominant
- Higher GS activity result in stiffness and limbness
- Present in more than 20 breeds
  - Most common in draft breeds of continental European breeds
  - Low allele frequencies in British drafts
  - **8% of warmbloods carry the mutation**
  - Rare to none existing in light breeds as xx and ox

Type 2:

- Unknown gene
- **92% of warmbloods with PSSM**
- Abnormal gaits and muscle pain
- Less likely to have tyed-up
- Normal levels of muscle glycogen

Microphthalmia & anophthalmia

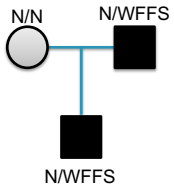
- One or both eyes missing or undeveloped
- Bi- or unilateral
- Probably autosomal recessive
- Many candidate genes
- Could be different mutations in different families



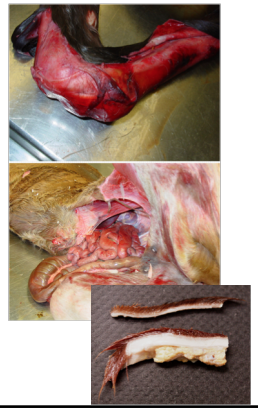
WFFS

Speculations or facts

- Many breeders look at pedigrees and try to figure out who are carriers
- Carriers with one parent tested as non-carrier will turn the other parent into an obliged carrier



Warmblood Fragile Foal Syndrome (WFFS)



- Symptoms:
  - Skin lesions
  - Extremely fragile and thin skin
  - Friable and very loosely attached to the underlying subcutaneous tissue
  - Subcutaneous oedema
  - Hematomas and seromas particularly in fetlocks and tarsus regions
  - Hyperextension of limb articulations
- Similar to HERDA
- Similar to Ehler-Danlos syndrome

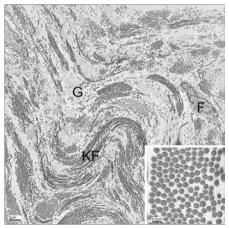
Monthoux et al. BMC Veterinary Research (2015) 11:12

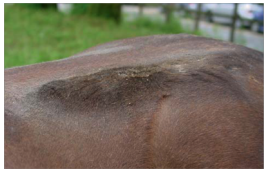
Hereditary Equine Regional Dermal Asthenia – HERDA

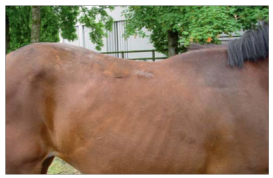
- First case reported in 1971
- 95% of the cases are traced back to the stallion Poco Bueno, the other 5% to his father and brothers
- 14% carriers among Quarter horses
- Autosomal recessive
- Mutation in the gene cyclophilin B (*PPIB*) => defect collagen α-molekyl
- Similar to Ehler-Danlos syndrome in humans

Case in Switzerland 2010

- Swiss Warmblod with HERDA-symptoms but no mutation in the HERDA gene *(PPIB)*
- Excluded Ehlers-Danlos syndrome type IV, VI, VIIA, VIIB och VIIC



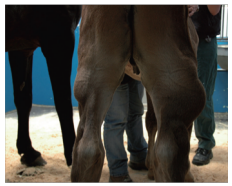


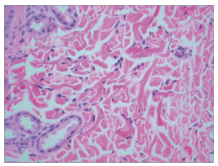


S. Rüfenacht et al., Band 152, Heft 4, April 2010, 188 – 192

Australian VETERINARY JOURNAL THE JOURNAL OF THE AUSTRALIAN VETERINARY ASSOCIATION LTD EQUINE

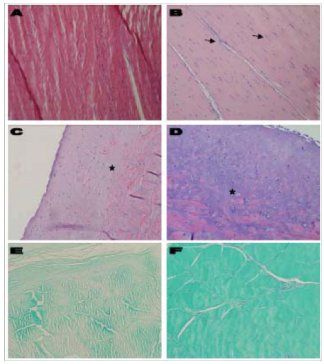
”Cutaneous asthenia” in a Warmblod foal (2011)





Marshall et al. Australian Veterinary Journal Volume 89, No 3, March 2011

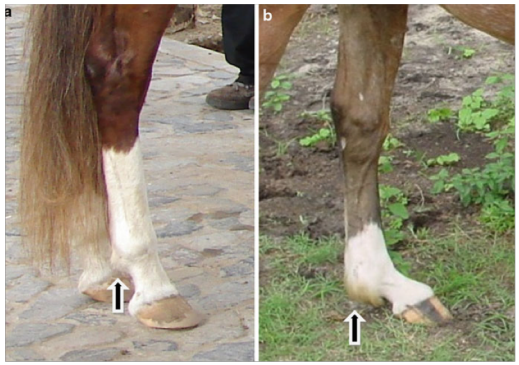
Degenerative Suspensory Ligament Desmitis



- DSLD (2011)
- Peruvian Paso and PP-crosses
- Until recently DSLD was considered to be a collagen defect limited to suspensory ligaments
- Systemic disease in tissues with high collagen content.
- Abnormal accumulation of proteoglycans also in superficial and deep digital flexor tendons, patellar and nuchal ligaments, aorta, coronary arteries and sclera in DSLD-affected horses

Halper J et al., 2011. Pak Vet J, 31(1): 1-8

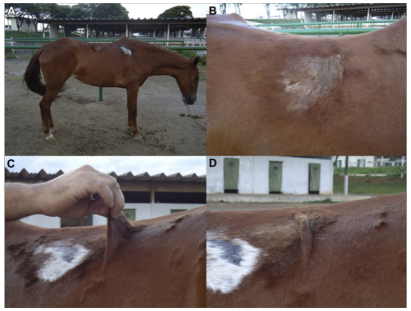
Degenerative suspensory ligament desmitis (DSLD)



= Equine Systemic Proteoglycan Accumulation (ESPA)

J. Halper (ed.), *Progress in Heritable Soft Connective Tissue Diseases*, Advances in Experimental Medicine 231 and Biology 802

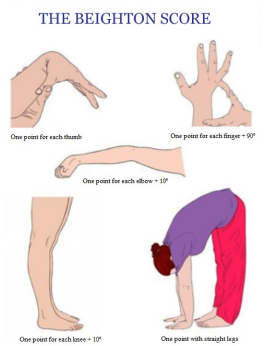
Ehler-Danlos affecting a Brasilian horse



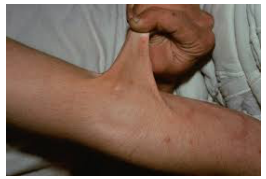
- Mangalarga-Campolino cross
- WFFS N/N
- HERDA N/N
- New mutation?
- One of the Ehler-Danlos subtypes?

J.P. Oliveira-Filho 96 et al. / Journal of Equine Veterinary Science 57 (2017) 95–99

Ehler-Danlos syndrome in humans



- Overly flexible joints
- Stretchy skin
- Fragile skin
- EDS fetuses of asymptomatic mothers affected by premature birth, still birth and abortion



Ehler-Danlos syndrome

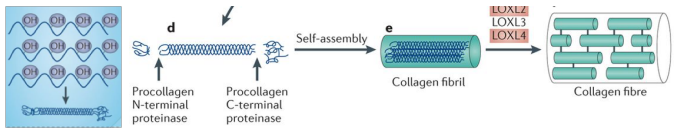
Sjukdom	Gen	Lokalisation	Genprodukt (protein)	Ärftlighet
Klassisk (cEDS)	*COL5A1* *COL5A2* *COL1A1*	9q34.3 2q32.2 17q21.33	kollagen typ V kollagen typ V kollagen typ I	AD
Klassisk-liknande (clEDS)	*TNXB*	6p21.33-p21.32	tenascin XB	AR
Cardiac-valvular (cvEDS)	*COL1A2*	7q21.3	kollagen typ I	AR
Vaskulär (vEDS)	*COL3A1* *COL1A1*	2q32.2 17q21.33	kollagen typ III kollagen typ I	AD
Arthrochalasia (aEDS)	*COL1A1* *COL1A2*	17q21.23 7q21.3	kollagen typ I kollagen typ I	AD
Dermatosparaxis (dEDS)	*ADAMTS2*	5q35.3	ADAMTS-2	AR
Kyfoskoliosis (kEDS)	*PLOD1* *FKBP14*	1p36.22	Lysylhydroxylas 1 FKBP22	AR

Sjukdom	Gen	Lokalisation	Genprodukt (protein)	Ärftlighet
Brittle Cornea Syndrom (BCS)	*ZNF469* *PRDM5*	16q24 4q27	ZNF469 PRDM5	AR
Spondylodysplastic (spEDS)	*B4GALT7* *B3GALT6* *SLC39A13*	5q35.3 1p36.33 11p11.2	Galactosyl transferas I Galactosyl transferas II ZIP13	AR
Musculocontractural (mcEDS)	*CHST14* *DSE*	15q15.1 6q22.1	Dermatan-4 sulfotransferas-1 Dermatan sulfat epimeras 1	AR
Myopathic (mEDS)	*COL12A1*	6q13-q14	Kollagen typ XII	AD eller AR
Periodontal (pEDS)	*C1R* *C1S*	12p13.31	C1r C1s	AD

WFFS is similar to EDS typ VI, kyphoscoliotic type (kEDS, Nemo syndrome)

The WFFS gene

- Autosomal recessive
- PLOD1 (lysyl hydroxylase 1)
- Cannot produce collagen (connective tissue)
- Old mutation



EDS in other species

- Cutaneous asthenia
- Dermatosparaxie

Esther van Praag, Medirabbit.com, Hansen et al. *Journal of Feline Medicine and Surgery (2015)* **17**, 954–963,

Do we need to panic?

Mutations in populations

Past

Present

Much of the original variation is lost by time

New variation added by mutation and migration

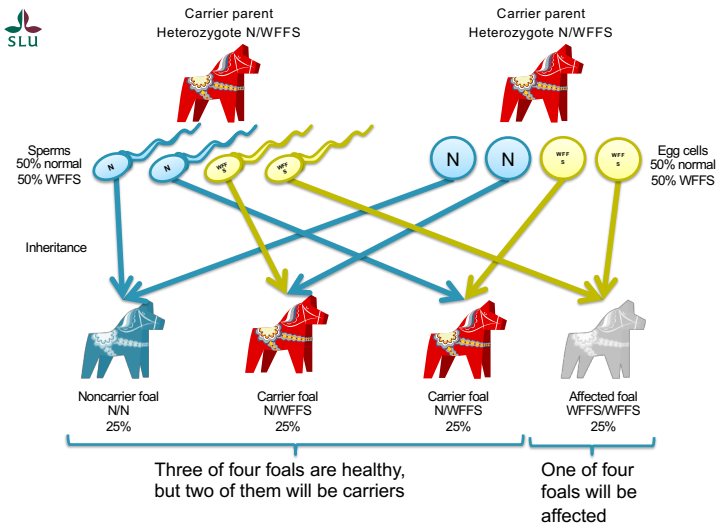
Carrier x Carrier cross

	N	WFFS
N	NN	N/WFFS
WFFS	N/WFFS	WFFS/WFFS

Carrier x Carrier cross

	N	WFFS
N	NN	N/WFFS
WFFS	N/WFFS	WF[illegible]FS

Dead foal



How large is the risk to have a WFFS foal?

10%

10% x 10% = 1% risk to cross two carriers

1% x 25% = 0,25% risk to have an affected foal

How large is the risk to have a WFFS foal?

20%

20% x 20% = 4% risk to cross two carriers

4% x 25% = 1% risk to have an affected foal

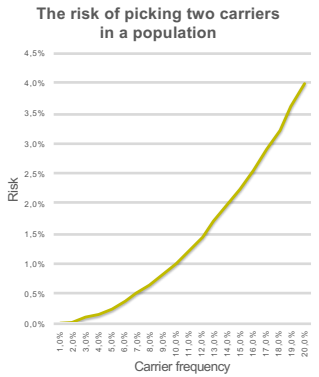
Carrier frequencies in USA

Veterinary Genetics Laboratory, UC Davis

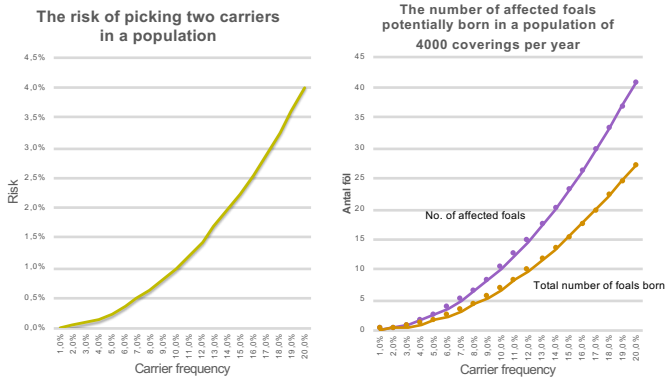
Breed	Number of tested horses	WFFS carriers
KWPN	104	7%
Hannoveraner	76	20%
Holsteiner	42	7%
Oldenburger	22	9%
~~Rheinland Pfalz-Saar~~	~~9~~	~~11%~~
~~SWB~~	~~7~~	~~0%~~
Trakhener	64	2%
~~Westphaler~~	~~7~~	~~14%~~
Totalt	**340**	**9%**

Few tested horses give unreliable frequencies

Risk of WFFS cases in a population



Risk of WFFS cases in a population



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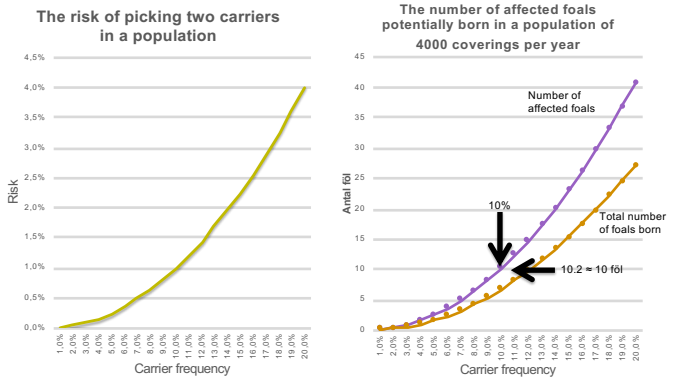
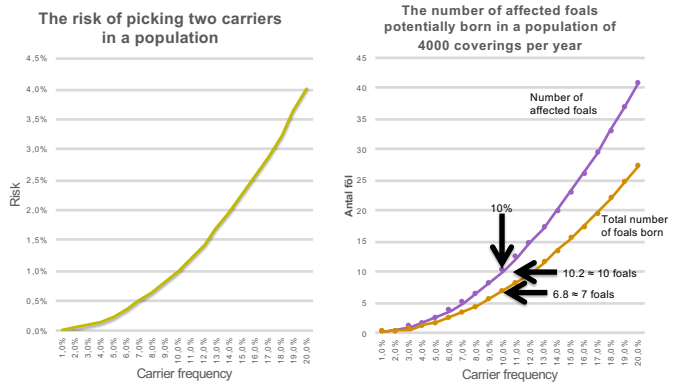
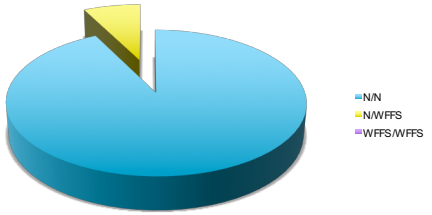


Risk of WFFS cases in a population



Frequency of carriers determine the potential number of affected foals



The frequency of the mutant allele in the population is approximately 1/2 of the carrier frequency.

Number of generations needed to reduce the frequency of a lethal mutation

Original allele frequency	New allele frequency	Number of generations
0,5	0,25	2
	0,1	8
	0,01	98
0,1	0,05	10
	0,01	90
	0,001	990
0,01	0,005	100
	0,001	900
	0,0001	9900

An undesirable mutation can quickly spread in the population

- If a well used stallion is carrier
- If a carrier has positive characteristics
- At a low frequency, the mutation is hidden in the population and is discovered when the frequency increases
- Unfavourable mutations are usually lost

Strategies in breeding

- To consider:
  - How large is the population?
  - How large is the effective population size?
  - How large is the genetic variation in the population?
  - Is the population inbred?
  - How strong is the selection, i.e. how large proportion of the population is used in breeding?
  - Is the studbook closed or open?
- There is a risk to decrease the genetic variation for other traits if all carriers are excluded from breeding
- WFFS-status is one of many characteristics to consider when selecting breeding individuals
- Never ever cross two carriers!
- Prioritize noncarriers in further breeding from a carrier parent

Test and inform!

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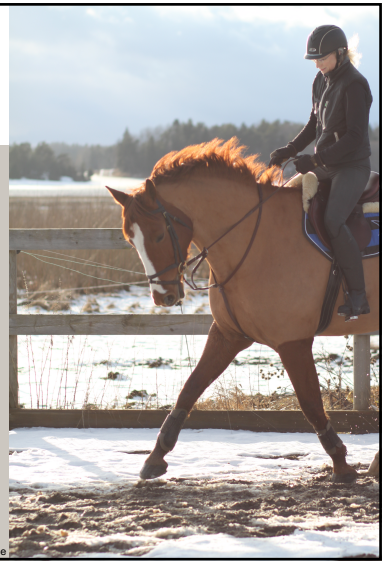
Thank You!



Coreograph (SWB) Photo: Carin Wrange