EFTBA Veterinary Newsletter 37

FFS

Fragile Foal Syndrome

Fig. 1 Fragile Foal Syndrome in a newborn foal

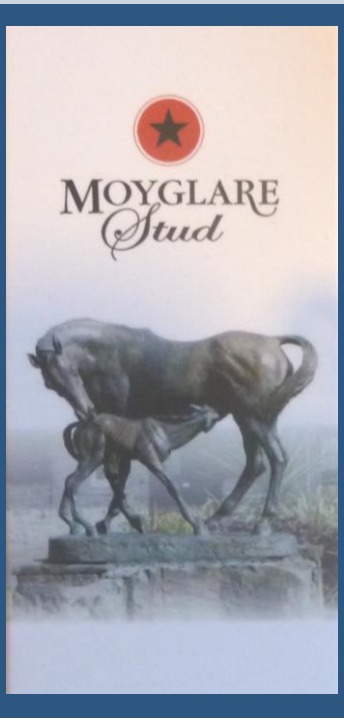
February 2021

. FFS is an inherited defect that causes connective tissue disorders

. The disease is present at birth and affected foals have to be euthanized

. The FFS mutation has been reported above all in warmbloods and is at a low frequency in Thoroughbreds

"Many thanks to Mrs. Eva-Maria Bucher-Haefner, Moyglare Stud Farm, for her valued sponsorship of this newsletter."



Welcome to EFTBA's veterinary newsletter

Dear EFTBA members,

Let me being by extending you all a belated Happy New Year.

It would not be an exaggeration to say that 2021 has gotten off to a very turbulent start; with BREXIT, COVID-19 and the upcoming Animal Health Law causing severe challenges and obstacles for breeders right across Europe. That said, your federation continues to lobby and negotiate at EU level on your behalf.

A meeting is scheduled to take place between EU Commissioner Ursula von der Leyen and the key EU Equine Stakeholders, at which Goran Akerstrom, Chairman of the IHSC Taskforce will be in attendance. Items to be discussed include BREXIT, EU Animal Health Law and VAT, which is a matter of high importance to all Thoroughbred breeders.

I would like to thank Hanspeter Meier for the latest EFTBA Veterinary Newsletter #37, which is very kindly sponsored by Moyglare Stud. In this edition Hanspeter rightly brings to our attention the serious matter of FFS (Fragile Foal Syndrome), which can be found in newborn foals. While this genetic disease is traditionally associated with warmblood breeds, cases of FFS have been identified in Thoroughbred foals in recent times. As guardian of the Thoroughbred, EFTBA should welcome all research into the emergence of FFS in newborn Thoroughbred foals.

We will keep all country members abreast of the outcome of the meeting with EU Commissioner Ursula von der Leyen.

In the meantime, I would like to take this opportunity to wish all European breeders a safe and successful 2021 breeding season. Hope springs eternal.

Best regards

Joe Hernon

Chairman, EFTBA

Editorial

Once more a newsletter with just an abbreviation in its title – and on top of this a problem of which the Thoroughbred breeder probably hasn't heard a lot of so far. – Luckily for us, but this genetic disease is a severe problem in many other breeds, above all Warmblood breeds, sorry to say.

However, by investigating this new disease in the last few years, Thoroughbreds recently also have been tested

research in this field must be very welcome and valuable for understanding both the nature of genetic diseases and their prevention.

Dr Hanspeter Meier
EFTBA veterinary advisor & Newsletter editor

Introduction

The birth of foals certainly is a most important part in the live of us breeders, and the disappointment is immens, if one is challenged by a sick neonate.

In the past, breeders and veterinarians occasionally came across newborn foals as shown on the front page (fig. 1), but the nature of cases as this one – FFS – only was discovered a few years ago (Winand 2011, Monthoux et al. 2015). One certainly was aware of resembling clinical pictures as for instance the Hereditary Equine Regional Dermal Asthenia (HERDA) in the American Quarter Horse, but the foal as above was tested negative for the mutation in the HERDA-responsible cyclophilin B gene (Rüfenacht et al. 2010) (s. annex).

5 years later, Monthoux et al. (2015) were more successful in testing an affected foal with comparable symptoms, and in this case, it proved to be the **syndrome of a mutation of the *PLOD1*-gene**. This gene is best-known in humanmedicine, where mutations of this gene are associated with the so called "**Ehlers-Danlos Syndromes**" (Type VI, kyphoscoliotic form) (s. annex).

This success led to very lively further research in equine medicine. Originally, this disorder was called "Warmblood Fragile Foal Syndrome" (WBFFS or WFFS), for the simple reason that this disease had mainly appeared in Warmblood-breeds. - But with the discovery of the disorder in other breeds as well, the term "Warmblood" and its abbreviation "W" have since been dropped (OMIA 2021).

All this work did also include investigations in the Thoroughbred and is therefore certainly also of great meaning and interest for us.

The discovery of the pathogenesis of FFS

It is just 10 years ago that Nena Winand (2011) in the USA identified "**the causative mutation for inherited connective tissue disorders in equines**" – the so-called *PLOD1* gene (which encodes **p**rocollagen-**l**ysine, 2-**o**xoglutarate 5-**d**ioxygenase **1**). It is one of the many genes which are also responsible for the Ehlers-Danlos Syndrome in humans.

The clinical proof of her outstanding work (case report) was published a few years later in Europe:

The first case-report

In 2015, Chloé Monthoux and co-workers presented a case-report with the title "Skin malformations in a neonatal foal tested homozygous positive for the Warmblood Fragile Foal Syndrome".

In the first place they made clear that only very limited data are available on the occurrence rate and clinical characteristics of this newly detected genetic disease in horses. However, some skin malformations already had been described in a variety of domestic animals during the last century as e. g. "cutis hyperelastica, hyperelastosis cutis, dermatosparaxis, dermal/collagen dysplasia, dermal/cutaneous asthenia or Ehlers-Danlos-like syndrome/s".

Their findings were: The Warmblood filly was homozygous positive for WFFA and was born with very thin, friable skin, skin lesions on the legs (fig. 2), the head, and had an open abdomen (fig. 3). These abnormalities required euthanasia just after delivery.

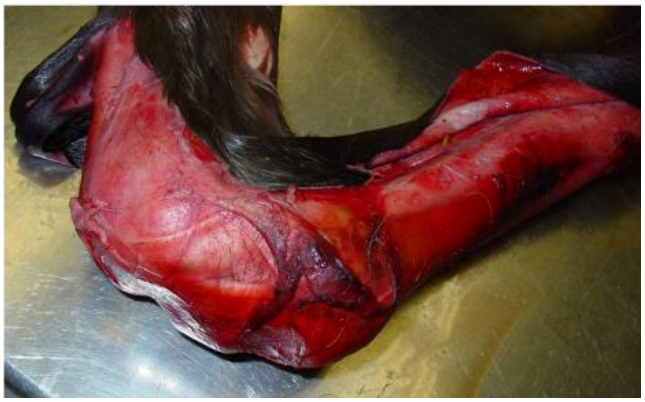


Fig. 2 Clinical presentation of the WFFS foal: The foal presented with severe ablation of skin on the right front leg …

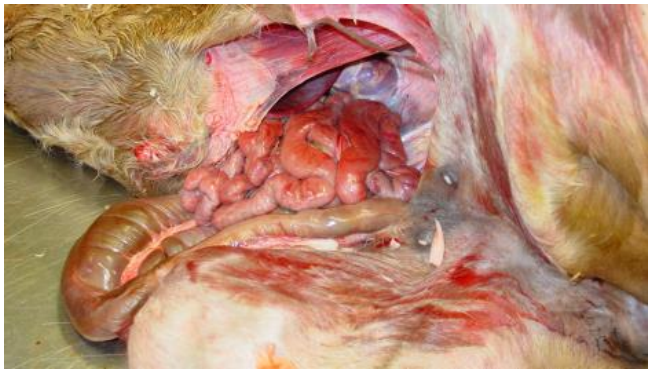


Fig. 3 … and an open abdomen with eventration of the small intestines (Monthoux et al. 2015)

The histologic examination revealed abnormally thin dermis, markedly reduced amounts of dermal collagen bundles, with loosely orientation and abnormally large spaces between deep dermal fibers.

Fig. 4 Skin morphology of the WFFS foal: Affected skin from the front limb (above) is markedly thinner (< 1.5mm) than unaffected skin from the back (below) of the same foal. (Monthoux et al. 2015)

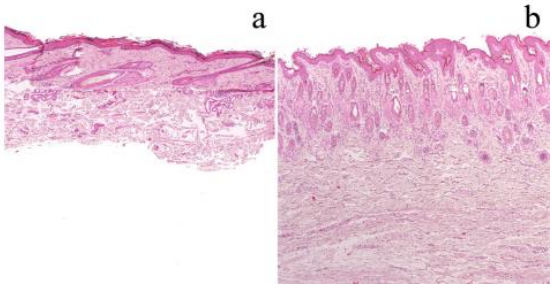


Fig. 5 Light microscopy of affected (a) and unaffected (b) skin: The deep dermis (a) is markedly thinned (approximately 30% of dermal thickness of hind limb skin of unaffected 1-day-old control Warmblood foal (b). It shows a reduced number of thin, irregular collagen bundles separated by clear spaces. Subcutaneous tissue was detached from the overlying dermis and is missing on this slide (a). (Monthoux et al. 2015)

Chloé Monthoux et al. (2015) did conclude that WFFS is a novel genetic disease in horses and should be considered in cases of abortion, stillbirth, skin lesions and malformations of the skin in neonatal foals.

They did recommend genetic testing of suspicious cases to evaluate the frequency of occurrence of clinical WFFS cases and its relevance for the horse population and noticed that, already in 2013, a DNA test had become available commercially through Laboklin GmbH & Co., Bad Kissingen, in Germany.

This advice was very well accepted and most interesting further studies followed – as for instance in Germany with its extraordinary Warmblood breeding stock.

Press release regarding WFFS

Especially the great interest of the German Warmblood breeders in FFS and its role for horse breeding was the driver for a larger national study. In the course of this joint initiative of the German studbooks, a team of the computation center IT Solutions for Animal Production (Vereinigte Informationssyteme Tierhaltung w.V. vit Verden) did address the questions of the overall role and the possible origin of FFS in the population of riding horses in Germany. This team made an immense effort for studying the pedigrees of about 15'000 horses (Wobbe et al. 2019). They followed the hypothesis that in consideration of the distribution of the mutation (e. g. in the USA, Switzerland, Sweden, Denmark and Germany), it already must have existed for quite some time. They also did consider that not only affected foals but also abortions might have been FFS-cases. Interestingly and in relation to the fact, that the mutation must have existed already for quite some time, one also wondered whether the carriers might have had a selection-advantage. – Could it have been a very popular stallion, whose descendants had been asked for in many countries? – In the opinion of us all, such reflections also had to answer the question whether a Thoroughbred stallion might have played a key role?

Therefore, one did consider TB-stallions at the begin of the last century. Finally, vit investigated about 2'000 pedigrees of FFS-carriers and came across *Dark Ronald,* a stallion which had been imported from England (1913, s. Annex). He was an outstanding sire in Germany, and after his death (1928, colic), his skin, heart and skeleton have been kept in the museum of the Martin-Luther-Universität Halle-Wittenberg. This allowed the very welcome chance to investigate his genome.

Skin exhibits of Dark Ronald xx are homozygous wild type at the Warmblood fragile foal syndrome

Zhang et al. (2020) grabbed this opportunity and the relicts enabled them to determine the genotype of *Dark Ronald* in somatic tissues. Their analysis provided evidence that he was **not** the founder of the WFFS causative variant. - That was also a most remarkable success, as Dark Ronalds' skin was tanned (Alter 2020, Zhang et al. 2020).

Further research concentrated than on a Hanoverian stallion (1861) and the objective of a further study was to validate the WFFST1 variant, to investigate the prevalence among the Hanoverian and other horse breeds and its association with performance and fertility traits.

Hanoverian F/W-line contributes to segregation of WFFS syndrome in Warmblood horses

For examining his presumption, Metzger et al. (2020) investigated the distribution of *PLOD1* among various horses in Europe, with particular focus on the Hanoverian breed. The study first referred to initial screenings in pedigree data which suggested *PLOD1*-mutation segregating among Hanoverian, Selle Francais, KWPN, Oldenburg and Westphalian breeds and the subsequent genetic testing proposed an allele frequency of 5.5% in Warmblood horses and **1.2% in Thoroughbreds** (Dias et al. 2019, Bellone et al. 2020).

The design of their investigation was a retrospectttive case-control and association investigation and aimed at identifying the origin of the mutant allele and also its correlation with performance and fertility traits in Warmblood horses. In total, 1166 blood or hair samples from 1059 horses, 76 ponies and 4 donkeys were obtained.

One used both **w**hole **g**enome **s**equencing (WGS) in 78 equids (77 horses of 35 breeds/populations and 1 donkey) and pathway analysis to trace back 81 carriers to the **m**ost **c**ommon **r**ecent **a**ncestor (MCRA).

The results showed that the WFFS variant T1 had the lowest minor allele frequency among all variants detected in the WGS data in the region of *PLOD1*. In Hanoverian horses, this variant revealed allele frequencies of 0.14.

Pathways analysis revealed a stallion from the Hanoverian sire F/W line as the most common recent ancestor of all tested genetic carriers. And, quite interestingly, this variant was also found to be correlated with estimated breeding values for gait-related traits as well as conformation and dressage (!); these findings certainly also ask for further research in warmblood-breeds.

Distribution of the WFFS Type 1 mutation in different horse breeds from Europe and the United States

Another study of last year (by researchers from Austria, Germany, Poland and California: Reiter et al. 2020) examined the distribution of the Warmblood Fragile Foal Syndrome Type 1 Mutation *(PLOD1)* in different horse breeds from Europe and the United States. They mentioned that homozygosity for the *PLOD1* variant has to date only been reported in warmblood breeds, but this allele had also been detected in the **Thoroughbred**.

To investigate the breed distribution of the WFFS allele, 4'081 horses belonging to 38 different breeds were screened. In total, 4.9% of the horses representing 21 breeds carried the WFFS allele. The affected breeds were mainly warmbloods, with carrier frequency as high as 17% in the Hanoverian and Danish Warmblood. The WFFS allele was not detected in most non-warmblood breeds. Exceptions included WFFS carriers in the **Thoroughbred** (17/716), Haflinger (2/48), American Sport Pony (1/12), and Knabstrupper (3/46).

In spite of the results of their brilliant research, the origin of the WFFS allele remains still unknown. The Arabian breed and specifically the stallion *Bairactar Or. Ar.* (1813), whose offspring were reported to have a similar phenotype in the 19th century, were hypothesized as the origin. But DNA from a museum sample (once more) of *Bairactar Or. Ar*. showed that he did **not** carry the mutated allele. This result, together with the genotypes of 302 Arabians, all homozygous for the reference allele, therefore does not support an Arabian origin of the WFFS allele.

This extensive survey shows the WFFS allele to be of moderate frequency and concern in warmbloods and also in breeds where it may not be expected.

WFFS type I Mutation is not associated with catastrophic breakdown and has a low allele frequency in the Thoroughbred breed

Finally – we certainly are especially interested in studies on Thoroughbreds, and a most interesting investigation was done by Bellone and co-workers (2020). Interesting above all for the reason, as they wondered whether the mutation of *PLOD1* might also have an influence on breakdowns in racing.

At first sight - one might wonder what the great problem of fragile foals could have in common with injuries on the racetrack? – But oh yes, quite a few reasons justify such a study. First of all, we must consider that the FFS is a fatal defect of connective tissue and that *PLOD1* is important for collagen biosynthesis in many body tissues, e. g. in cross-linking of collagen fibrils, the 'building blocks' of tendons and many other structures. Moreover, one also knows for instance the so-called "Equine Systemic

Proteoglycan Accumulation" (ESPA s. annex) in many breeds, best known as the reason for the degenerative suspensory ligament desmitis. ESPA is also a systemic disease of the connective tissue of the horse and mule and is also akin to the Ehlers-Danlos syndromes(!).

The researchers in the US therefore aimed to determine whether the *PLOD1* allele frequency differs between cohorts of Thoroughbred horses known to have catastrophic injuries during a race or in training, compared with those raced with no record of injury, and those not raced (catastrophic breakdown n=22, no record of injury at the same track and season n=138, TBs older than 7 years and raced during the same season n=185, non-racers n=92, and a random sample without consideration for racing history n =279 [altogether n=716]).

The methods were sampling genomic DNA from hair and/or tissue samples and genotyping for the WFFS allele.

Their results showed, that the WFFS allele was detected in all these cohorts at a low frequency ranging from 0.5 to 1.8%. Among all samples, the allele frequency was 1.2%. Of the 716 horses tested in this study, **17 were carriers** for the deleterious allele (2.4%) and **no horses homozygous** for the variant allele were identified. In the 22 catastrophic breakdown cases, only **one single horse** carried the *PLOD1c.2032G>A* allele. No statistically significant difference in allele or carrier frequency was identified between case and control cohorts in all comparisons performed.

Conclusions: This study demonstrated that the *PLOD1c.2032G>*A associated with WFFS is present at a very low frequency in Thoroughbreds and is not a genetic risk factor for catastrophic breakdown.

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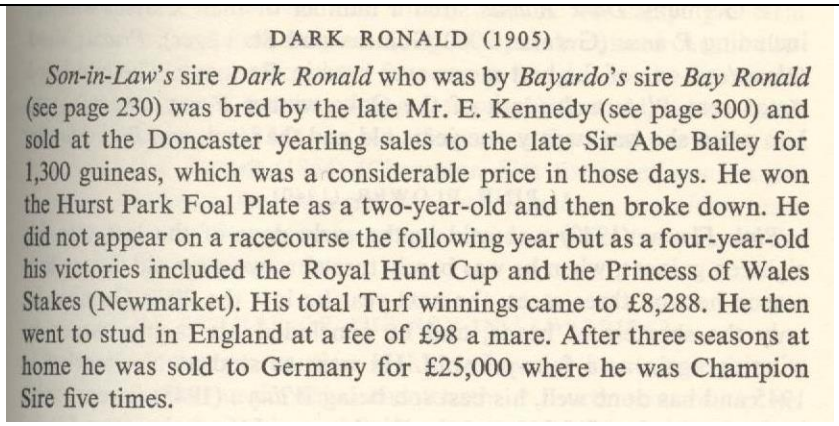
Annex

Dark Ronald



DARK RONALD (1905)

Son-in-Law's sire *Dark Ronald* who was by *Bayardo's* sire *Bay Ronald* (see page 230) was bred by the late Mr. E. Kennedy (see page 300) and sold at the Doncaster yearling sales to the late Sir Abe Bailey for 1,300 guineas, which was a considerable price in those days. He won the Hurst Park Foal Plate as a two-year-old and then broke down. He did not appear on a racecourse the following year but as a four-year-old his victories included the Royal Hunt Cup and the Princess of Wales Stakes (Newmarket). His total Turf winnings came to £8,288. He then went to stud in England at a fee of £98 a mare. After three seasons at home he was sold to Germany for £25,000 where he was Champion Sire five times.

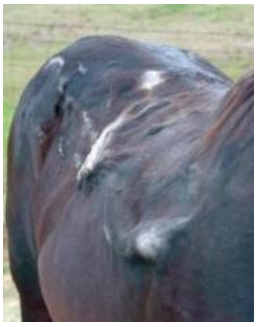
Sir Charles Leicester (1957): Bloodstock Breeding

Pedigree of Dark Ronald (GB), B.h. 1905

Sire Bay Ronald b. 1893	Hampton b. 1872	Lord Clifden b. 1860	Newminster
			The Slave
		Lady Langden br. 1868	Kettledrum
			Haricot
	Black Duchess br. 1886	Galliard br. 1880	Galopin
			Mavis
		Black Corrie blk. 1879	Sterling
			Mare by Wild Dayrell
Dam Darkie blk. 1889	Thurio br. 1875	Cremorne b. 1869	Parmesan
			Rigolboche
		Verona ch. 1854	Orlando
			Iodine
	Insignia b. 1882	Blair Athol ch. 1861	Stockwell
			Blink Bonny
		Decoration br. 1873	Knight of the Garter
			Toison D'Or (F-No.9b)

Dark Ronald was incredibly influential in warmblood breeding, especially in the Holstein breed. Cor de la Bryère, Lord, and Landgraf I were all linebred to him.
Other influential sires with Dark Ronald blood include:
Furioso: (sire of 10 Olympic contenders in the Tokyo Games, and 30 international winners)
Cottage Son: grandson of Dark Ronald and an influential sire in warmblood breeding
Ladykiller xx
Cor de la Bryère: the great jumping sire, through his sire Rantzau
Landgraf I
Beau Pere: exported to New Zealand and later to America, he influenced the breeding of racehorses, jumpers, and eventers. Progeny include Mary Chapot's White Lightning, Katie Monahan's Encore, Kerry

	Milikin's eventer Landlady, Sundancer (two-time winner of the American Invitational), Easy Doc (a member of the Canadian equestrian team), and Turn on the Sun (part of the British equestrian team). Der Löwe Abendfrieden: great-grandson of Dark Ronald, sired the great Pik As Bolero: dressage stallion, sire of Brentano II, who sired Brentina and was grandsire of Poetin, foundation sire of a new B-line. My Babu: great racehorse sire, also sired several phenomenal eventers, including Babu Dancer, sire of Bruce Davidson's mount JJ Babu (Wikipedia)
Ehlers-Danlos Syndromes (human-medicine)	Ehlers–Danlos syndromes (EDS) are a group of rare genetic connective-tissue disorders. Symptoms may include loose joints, joint pain, stretchy velvety skin, and abnormal scar formation. These can be noticed at birth or in early childhood. Complications may include aortic dissection, joint dislocations, scoliosis, chronic pain, or early osteoarthritis. EDS occur due to variations of more than 19 different genes that are present at birth. The specific gene affected determines the type of EDS. Some cases result from a new variation occurring during early development, while others are inherited in an autosomal dominant or recessive manner. Typically, these variations result in defects in the structure or processing of the protein collagen. This group of disorders affects connective tissues across the body, with symptoms most typically present in the joints, skin, and blood vessels. Effects may range from mildly loose joints to life-threatening cardiovascular complications. Due to the diversity of subtypes within the EDS family, symptoms may vary widely between individuals diagnosed with EDS. In 2017, 13 subtypes of EDS were classified using specific diagnostic criteria. Diagnosis is often based on symptoms and confirmed with genetic testing or skin biopsy. Genetics: Almost every type of EDS can be positively tied to specific genetic variation. Variations in these genes can cause EDS: Collagen primary structure and collagen processing: ADAMTS2, COL1A1, COL1A2, COL3A1, COL5A1, COL5A2 Collagen folding and collagen cross-linking: PLOD1, FKBP14 Structure and function of myomatrix: TNXB, COL12A1 Glycosaminoglycan biosynthesis: B4GALT7, B3GALT6, CHST14, DSE Complement pathway: C1R, C1S Intracellular processes: SLC39A13, ZNF469, PRDM5 Variations in these genes usually alter the structure, production, or processing of collagen or proteins that interact with collagen. Most forms of EDS are inherited in an autosomal dominant pattern, which means only one of the two copies of the gene in question must be altered to cause a disorder. No cure is known. (Wikipedia)
ESPA (DSLD)	Equine Systemic Proteoglycan Accumulation (in earlier times also called Degenerative Suspensory Ligament Desmitis (DSLD), is a systemic disease of the connective tissue of the horse and other equines. It is a disorder akin to Ehlers–Danlos syndromes being researched in multiple horse breeds. Originally thought to be a condition of overwork and old age, the disease is now recognized as hereditary and has been seen in

	horses of all ages, including foals. The latest research (2010) has led to the proposed renaming of the disease from DSLD to ESPA because of the systemic and hereditary components now being found. It has been found in many horse breeds, including Arabians, Thoroughbreds, American Quarter Horses, Morgans, Peruvian Pasos, Paso Finos, American Saddlebreds, several breeds of warmblood, Appaloosas, Friesians, Missouri Fox Trotters, Tennessee Walkers, American Paint Horses, National Show Horses, and Mustangs, as well as crossbreds and mules. ESPA was once considered a condition of the legs only, as one of the most visible signs is when the fetlocks, particularly on the hind legs, collapse into a "coon-footed" position. However, microscopic examination in necropsy has shown ESPA horses can not only be affected in the tendons and ligaments of all legs and the patella, but can have affected tissues in the nuchal ligament, eyes, aorta, skin and fascia, lungs and other organs, as well as ligaments and tendons throughout the body. Because of its systemic nature, and because connective tissue is present everywhere in a biological entity, the entire body becomes affected in multiple ways as the disease progresses. Ongoing research is working on the biochemical aspects of the disease and it is strongly believed to be passed genetically, and those aspects are being studied in the search for a DNA marker. (Wikipedia)
HERDA 	Hereditary equine regional dermal asthenia (HERDA) is a genetic skin disease predominantly found in the American Quarter Horse. HERDA is characterized by hyperextensible skin, scarring, and severe lesions along the back of affected horses. Affected foals rarely show symptoms at birth. The condition typically occurs by the age of two, most notably when the horse is first being broke to saddle. There is no cure, and the majority of diagnosed horses are euthanized because they are unable to be ridden and are inappropriate for future breeding. HERDA has an autosomal recessive mode of inheritance and affects stallions and mares in equal proportions. Research carried out in Dr. Danika Bannasch's laboratory at the University of California, Davis, identified the mutation causing HERDA. HERDA is caused by a single base change in the gene *PPIB* (c.115G>A). *PPIB* is one of the proteins involved in proper collagen formation. Collagen is an important structural protein of all connective tissues including skin. Functional studies have shown that the HERDA mutation delays proper collagen folding and secretion and is presumed to alter collagen organization thus leading to the clinical manifestations. (UC Davis Veterinary Genetics Laboratory)

If there is any area you would like covered in these very informative newsletters you should contact Kerry on kryan@itba.ie and she will forward your request on.

Joe Hernon, Chairman EFTBA

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