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Fragile Foal Syndrome: Its Past, Present, and Future

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Fragile Foal Syndrome: Its Past, Present, and Future

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for the Murray State University Honors Diploma

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Abstract

Though Fragile Foal Syndrome (FFS) has been around for some time, the public interest in FFS is recent. The hype spread rapidly from a public media announcement that a stallion at a prominent North American stud farm was a carrier (Brooks, 2021). As with most genetic mutations, FFS likely arose due to the increased inbreeding that results from human selection (Orlando & Librado, 2019). Fragile Foal Syndrome affects the enzyme responsible for developing the connective tissues. Two recent case studies highlighted the devastating effect of FFS on every part of the equine body (Metzger, et al., 2020; Grillos, 2021). So far, no one knows for sure where the mutation originated, but the strongest theory is that the origin lies with the Thoroughbred and its progenitors (Brooks, 2021). Future advances in reproductive technologies and techniques could reduce the need to worry about the effects of harmful mutations on the equine population. These techniques come with ethical issues, but the majority of breeders are determined to err on the side of caution. They, along with registries and other interest groups, are taking steps to promote public education and curb the spread of FFS.

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Introduction

Though Fragile Foal Syndrome (FFS) has been around for some time, the hype around FFS is recent. The interest spread rapidly from a public media announcement that a stallion at a prominent North American stud farm was a carrier (Brooks, 2021). As with most genetic mutations, FFS likely arose due to increased inbreeding further exacerbated by the formation of closed studbooks in the last two centuries (Orlando & Librado, 2019). Fragile Foal Syndrome affects the enzyme responsible for developing the connective tissues. Researchers believe that the majority of affected foals miscarry during gestation. Those that survive till birth have to be euthanized shortly after (Rowe, 2021; Grillos, 2021). Two recent case studies involved necropsies on an affected Warmblood filly, and the first confirmed affected Thoroughbred foal. Both cases highlighted the devastating effect of FFS on every part of the equine body (Metzger, et al., 2020; Grillos, 2021). The recent public interest in FFS led to research into the mutation's prevalence within the equine population. DNA studies showed that the FFS mutation is present mainly in Warmbloods, though it has been found in other, unrelated breeds (Grillos, 2021). So far, no one knows for sure where the mutation originated, but various theories exist. The strongest theory lies with the Thoroughbred and its progenitors since Thoroughbreds heavily influenced the development of the Warmblood types (Brooks, 2021). Further research is still forthcoming, but current results indicate that carriers of the mutation could receive a competitive benefit for dressage from increased flexibility and freedom of movement (Ablondi, et al., 2021). Future advances in reproductive technologies and techniques, such as gene editing and Intracytoplasmic Sperm Injection (ICSI), could

reduce the need to worry about the effects of harmful mutations on the equine population. However, these techniques come with ethical issues. Where does the equine industry draw the line between competitive advantage, animal welfare, and natural genetic variation? The majority of breeders are determined to err on the side of caution. They, along with registries and other interest groups, are taking steps to promote public education and curb the spread of FFS.

Genetics and Heritability

Every gene in the body has its particular position, referred to as a locus, on a chromosome.[1] Every gene is coded for by DNA comprised of "organic bases" joined in a certain order. Adenine and guanine are called the "purine bases," and cytosine and thymine are called the "pyrimidic bases." A single gene's sequence can have as many as 1000 base pairs.[2] Each gene is subdivided into two alleles, one of which is transmitted to any offspring.[3] These individual alleles are the possible variations within each given gene. The particular combination of alleles inherited by offspring determines the visible phenotype.[4]

The genetic influence of stallions on their future descendants cannot be understated. The Y chromosome does not undergo recombination between inheritance cycles, so it is an excellent map of the demographic and migratory history of male ancestors. Studies of the Y chromosome show that, besides a small number of northern European haplotypes, the entirety of modern horse breeds falls into an approximately 700-year-old haplogroup brought to Europe via "Oriental" stallions. This "Oriental" group has two major categories – Arabian and Turkoman. Research has shown that the

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[1] Bailey, E., Brooks, S. (2020). *Horse Genetics 3rd Edition* (3rd edition). CAB International. 10.1079/9781786392589.0000

[2] Roy, R. N. (2011). *Heredity, Genetics, and Genetical Diseases.* New Central Book Agency Ltd.

[3] Bailey, E., Brooks, S. (2020). *Horse Genetics 3rd Edition* (3rd edition). CAB International. 10.1079/9781786392589.0000

[4] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

Thoroughbred is descended from Turkoman lines, and the Thoroughbred, in turn, is largely responsible for the prevalence of this haplotype in the modern horse. Also responsible was the popularity from the 16th to the end of the 18th century of importing "foreign" stallions to cross with the local horse population (Wallner et al., 2017).

Since the sequencing of the equine genome in 2006, equine genetics has grown by leaps and bounds. With the ability to sequence and study the equine genome, scientists have analyzed DNA from ancient, fossilized horses, the oldest of which is approximately 70,000 years old. Two discoveries researchers made from this feat are that ancient horses had more diversity in their genome than modern domesticated horses, and they had fewer potentially lethal recessive mutations due to a high number of heterogeneous genomes (Brooks, 2021).[5] Scientists term this increase in the number of possibly lethal mutations the "cost of domestication" (Bailey, 2015, p. 364). Natural selection ensures the lack of traits deleterious to survival with brutal efficiency. Artificial breeding practices have narrowed the gene pool and allowed for the increase in harmful genes (Bailey, 2015). Successful and popular stallions are a frequent source of the prevalence of genetic disorders. The high numbers of offspring and resultant linebreeding/inbreeding to try to accumulate the desired trait can rapidly spread the problem.[6]

Around one hundred fifty years ago, the monk and botanist Gregor Mendel made the observations that became the "basic laws of inheritance."[7] Mendel utilized pea plants

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[5] Leatherdale Equine Center (n.d.). *Simple versus complex genetic diseases*. University of Minnesota College of Veterinary Medicine. https://www.equine.umn.edu/node/346

[6] Leatherdale Equine Center (n.d.). *Simple versus complex genetic diseases*. University of Minnesota College of Veterinary Medicine. https://www.equine.umn.edu/node/346

[7] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

in his experiments because they have simple and easily noticed traits that can be tracked in any offspring.[8] From these experiments, Mendel made his conclusions about how characteristics are passed from one generation to the next. Mendel's first conclusion came to be known as the "Law of Segregation." This law states that "the characteristics of an organism are controlled by genes occurring in pairs. Of a pair of such genes, only one can be carried in a single gamete." Later research and the discovery of the process of meiosis confirmed Mendel's conclusion.[9] Mendel's "Second Law of Inheritance" is known as the "Law of Independent Assortment." It is a continuation of the first law and holds that "each member of a pair of alleles may combine randomly with either of another pair."[10] Mendel's experiments consisted of traits governed only by one gene, so Mendelian inheritance is only the simple tip of the complex genetics iceberg.[11]

As with Mendel and his pea plants, traits governed only by a single gene are where the most advances in genetics have been made, as they are the simplest to understand the mechanics of and to test for. As of this study, there are 14 genetic diseases, 15 coat colors, and 2 performance traits in equines that have genetic tests. However, most of the performance traits that breeders are primarily interested in, speed, stamina, etc., are governed by complex inheritance, involving multiple genes and various factors (Bailey, 2013).

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[8] Roy, R. N. (2011). *Heredity, Genetics, and Genetical Diseases.* New Central Book Agency Ltd.
[9] Roy, R. N. (2011). *Heredity, Genetics, and Genetical Diseases.* New Central Book Agency Ltd.
[10] Roy, R. N. (2011). *Heredity, Genetics, and Genetical Diseases.* New Central Book Agency Ltd.
[11] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

Dominant Genes

A dominant allele is able to mask the presence of a recessive gene in the heterozygous form.[12] Unlike recessive alleles, only one copy of a dominant gene needs to be present to express that gene in the phenotype.[13] Incomplete dominance is when a dominant allele is not quite dominant enough to mask the presence of the recessive gene entirely. The resultant phenotype will reflect a hybrid of the two alleles.[14] Co-dominance is when both alleles' phenotypes are fully expressed. Blood types are a common example of incomplete dominance. Each parent can have a different type, while the offspring's type consists of both of the parent's types.[15]

Recessive Genes

Recessive alleles can only be expressed phenotypically when two copies of the recessive allele are present.[16]As with simple dominant genes, recessive genes are often spoken of together with predictive Punnett squares and Mendelian genetics. Punnett squares are useful for predicting the distribution of alleles for simple inheritance, including with diseases. Recessive mutations do not manifest with only one copy of the allele because the healthy allele can make up for the deficit. Homozygosity for the recessive alleles means that there is no healthy allele to compensate, and the disease is

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[12] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.
[13] Austin, C. P. (n.d.). *Dominant*. National Human Genome Research Institute. https://www.genome.gov/genetics-glossary/Dominant
[14] Robinson, T., Spock, L. (2020). Genetics for Dummies (3rd Edition). Wiley Publishing, Inc.
[15] Roy, R. N. (2011). *Heredity, Genetics, and Genetical Diseases.* New Central Book Agency Ltd.
[16] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

able to manifest.[17] Fragile Foal Syndrome is an autosomal recessive disease. Autosomal refers to the fact that the gene is not located on the sex chromosomes.[18]

Gene Mutations

Dominant harmful mutations are less common than their recessive counterparts because they only require one allele to manifest. This means that the disorder will always be inherited by the offspring, and before domestication, natural selection would ensure that those affected most likely would not live to produce affected offspring of their own. With modern breeding practices, being dominant makes it easy for breeders to make culling decisions, as opposed to recessive traits where breeding carriers only has a 25% chance of producing an affected foal (Orlando & Librado, 2019). Thus, debilitating or deadly alleles are nearly always recessive and appear only in the homozygous state.[19] "Wild-type" refers to the "normal" phenotype that would be seen in the wild without human intervention and is generally dominant. Any changes from this are mutations, which include both harmful and neutral changes.[20]

Heritability refers to the ability of a "sequence variant" to be passed from parent to offspring.[21] These variations are either Somatic or Germ-cell variants. Somatic variants are changes in somatic cells, which comprise the majority of the body's cells. These changes cannot be passed to offspring. Germ-cell variants are changes in the body's germ

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[17] Austin, C. P. (n.d.). *Recessive*. National Human Genome Research Institute. https://www.genome.gov/genetics-glossary/Recessive

[18] Hart, S. (n.d.). *Autosomal Dominant*. National Human Genome Research Institute. https://www.genome.gov/genetics-glossary/Autosomal-Dominant

[19] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

[20] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

[21] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

cells. These changes can be passed to offspring because germ cells are ultimately responsible for embryo formation.

Mutations in DNA occur frequently and randomly. A change is considered normal or polymorphic if the result is a functioning protein that does the job it is supposed to complete. A change is referred to as a functional change when the result is a protein that does something different. There are further categories within functional changes. “Gain-of-function” variations produce proteins that either perform better than before or have an entirely different function. These variations are usually passed to offspring as a dominant allele. “Loss-of-function” variations produce proteins that either cease to function or have severely altered functions and are inherited as recessive traits. The majority of genetic disorders, including FFS, are “loss-of-function” changes in the DNA. The generally recessive nature of most genetic disorders is the reason that carriers of the disease live unaffected lives. The unchanged, normally functioning allele capably does the job of both alleles.[22]

[22] Robinson, T., Spock, L. (2020). *Genetics for Dummies* (3rd Edition).Wiley Publishing, Inc.

Breeding Practices

Outcrossing

Outcrossing involves breeding animals within a breed whose pedigrees do not share a common ancestor for at least four to six generations, though ideally, they would not have any common ancestors.[23] The purpose of crossing unrelated animals is to increase the number of unique alleles in the resultant offspring. A high number of different alleles produces offspring that tend to be fitter and healthier than their more inbred counterparts.

Linebreeding

Linebreeding is very similar to inbreeding in that it involves breeding related individuals. However, the relationship is not quite as close and generally not as extreme. The goal is to preserve a relationship with a desirable ancestor rather than simply crossing successful individuals and their offspring hoping to compound their success.[24] This desired ancestor generally appears no closer than the fourth generation and frequently in the fifth and sixth generations. By inbreeding further back in the pedigree, the resultant offspring ideally will have a higher measure of the successful genotype and less chance of inheriting any troublesome genes.

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[23] Ensminger, M. E. (1972). *Breeding and Raising Horses.* United States Department of Agriculture.
[24] Ensminger, M. E. (1972). *Breeding and Raising Horses.* United States Department of Agriculture.

Linebreeding is an endeavor that requires patience. With each successive generation, a particular animal's genetic influence decreases by half. Linebreeders get around this by using "prepotent" ancestors who are known to pass on their traits in a predictable fashion. Another method is to cross a linebred animal with another animal that has the desired or a complementary ancestor closer in the pedigree.[25]

Inbreeding

Inbreeding is the term used to refer to the breeding of related individuals in the hopes of increasing desirable traits in the resultant offspring. An inescapable side effect of inbreeding is the increased possibility for the expression of harmful recessive genes because of the decreased genetic variety in the next generation. However, inbreeding coefficients cannot be determined simply by examining pedigrees. Siblings do not usually inherit the same alleles from their parents, so the inbreeding coefficient of each animal may not come from the same ancestor (Poyato-Bonilla, et al., 2020). The end goal of inbreeding is increased homozygosity that produces "true-breeders" – lines that consistently pass along one or more desired characteristics to their offspring. Successful inbreeding does require rigorous culling, which can be economically stressful when you can only produce one offspring per female animal per year.[26]

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[25] Passman, S. (2002). Linebreeding, Inbreeding, Close Breeding. *Impulsion*, Fall 2002, pp. 8-21. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.83.2331&rep=rep1&type=pdf

[26] Passman, S. (2002). Linebreeding, Inbreeding, Close Breeding. *Impulsion*, Fall 2002, pp. 8-21. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.83.2331&rep=rep1&type=pdf

The Thoroughbred is an excellent breed in which to study both the beneficial and the harmful effects of inbreeding for two reasons. They are one of the largest closed animal populations in the world, and all Thoroughbreds are descended from only three sire lines. Artificial breeding selection heavily favors lines with desirable traits, and less successful lines are left to die out, leading to decreasing genetic diversity. Unfortunately, these lines with desirable traits often come with undesirable traits that increasingly appear as the amount of inbreeding increases. Records indicate that the grandsire of the great stallion Eclipse likely suffered from exercise-induced pulmonary hemorrhage. The stallion Touchstone, a leading British sire in the mid-1800s, reportedly had various conformational and behavioral problems (Todd, et al., 2018).

"Genetic load" refers to the undesirable genes in a population and has an inverse correlation to the fitness level of the same population (Todd, et al., 2018). Studies indicate that the number of harmful mutations was fairly low and widely dispersed until around 250 years ago and the advent of closed studbooks. Closed studbooks limit the number of breeding animals and lead to decreased genetic diversity. The advent of the car and the tractor rendered horses almost unnecessary for travel and growing food in more developed countries and resulted in drastic population drops that further decreased genetic diversity. Studies have revealed that there has been an approximately 16% decrease in genetic heterozygosity and an approximately 4% increase in mutations in the last 200 years (Orlando & Librado, 2019; Fages, et al., 2019). Prior to 200 years ago, equine populations maintained consistent levels of heterozygosity and higher levels of genetic diversity for four millennia (Fages, et al., 2019). The United Nations Farm Animal Organization recommends that breeds be maintained with no more than 1%

accumulation of inbreeding with each generation (Dell, et al., 2021). This requires breeders to institute better breeding practices to make it happen.

The main method of avoiding the negative effects of inbreeding is simply not to breed related, or at least only breeding minimally related, individuals, utilizing genealogical and, if available, genetic data. Recently, researchers have put forward two other methods for reducing inbreeding depression – purging and genetic rescue.

Purging can occur naturally and artificially. Artificial purging involves deliberately inbreeding and keeping only the offspring that are not affected. However, this would lead to a decrease in fitness levels before any benefits became apparent and, if continued long-term, would only start the problem all over again.

Genetic rescue involves bringing in genetic material from an entirely unrelated individual or individuals. There are a couple of problems with this. The new individual or individuals would need to be phenotypically similar to the population needing help. Also, even if genetic variety is successfully increased, the population must be carefully managed to avoid dangerous levels of inbreeding starting all over again (Hedrick & Garcia-Dorado, 2016).

Recessive Genetic Diseases Similar to Fragile Foal Syndrome

Fragile Foal Syndrome (FFS) is not the only recessive disorder in horses affecting the skin and connective tissues. Hereditary Equine Regional Dermal Asthenia (HERDA) is a disorder similar to Ehlers-Danlos Syndrome that primarily affects Quarter Horses, Appaloosas, and Paints (Grillos, 2019; Rashmir-Raven, 2013). The first reports about HERDA appeared in literature around 1978. Similar to FFS, HERDA is inherited recessively and affects the proper production of collagen (Rashmir-Raven, 2013). Phenotypical manifestation includes hematomas, skin ulcers, and hypersensitive skin (Grillos, 2019). The trademark sign of HERDA is loose skin that easily moves and does not appear to be connected to the horse. The most acute cases can include skin sloughing and lacerations from minor injuries, which lead to severe scarring (Rashmir-Raven, 2013). Clinical signs of HERDA differ from those of FFS in that they are generally not seen at birth but develop later in life (Grillos, 2021). The average appearance of the first signs is around two years of age (Aurich, 2019). Cutting-bred Quarter Horses have the highest prevalence of HERDA, but it also appears in western pleasure, reining, working cow, and foundation-bred horses. Hereditary Equine Regional Dermal Asthenia llustrates the significance of sires to the spread of harmful alleles. In 2012, three of the ten leading lifetime sires of cutting horses were confirmed carriers and had a total of 5,792 offspring, half of which are either carriers or affected (Rashmir-Raven, 2013). There is no known treatment, although some factors have been shown to reduce the severity of symptoms. Keeping the affected horse in a stall, using a UV flysheet when outdoors, and moving the

horse to a cooler, northern climate have been shown to decrease the severity of symptoms in some cases (Rashmir-Raven, 2013).

Junctional Epidermolysis Bullosa (JEB) is a recessive disorder where the mutation causes splits in the skin due to a lack of the components and fibers that keep the layers of skin together. Skin lesions are either present at birth or appear soon after. Lesions quickly develop into ulcers and erosion of the skin at sites including oral mucosa, lips, extremities, and the coronary band. Erosion of the coronary band can end with sloughing of the hoof, and infections at other injury sites are common. The two causative mutations are located within two different genes responsible for coding for a “Laminin 332 protein complex”. An insertion in the LAMC2 gene is causative for draft horses, and a deletion in the LAMA3 gene is causative in Saddlebreds. A genetic study of the first suspected case of JEB in an Italian Draft Horse showed that the foal was homozygous for the LAMC2 insertion, confirming that the breed now joins the Belgian, Trait Breton, and Trait Comtois as affected European draft breeds (Cappelli, 2015).

What is Fragile Foal Syndrome?

An autosomal recessive disorder, Fragile Foal Syndrome (FFS) is caused by a single mutation in the nucleotide sequence of the *procollagen-lysine-2-oxoglutarate-5-dioxygenase 1* (PLOD1) gene (Reiter, et al., 2020; Grillos, 2021). This mutation prevents the correct formation of the enzyme lysyl hydroxylase, which aids in the interconnection of collagen fibers. The resulting enzyme deficiency causes instability of the connective tissues (Rowe, 2021). Prior to 2021, FFS was referred to as Warmblood Fragile Foal Syndrome because the only confirmed affected births occurred in Warmbloods. However, only 18 confirmed cases have been reported in Warmbloods, despite a high carrier frequency – up to 17% in some populations (Grillos, 2021).

Fragile Foal Syndrome is very similar to Ehlers-Danlos Syndrome (EDS) in humans. EDS is a grouping of connective tissue disorders characterized by hypermobility of the joints and very stretchy and fragile skin. Researchers have identified mutations in twenty different genes that cause EDS, including the PLOD1 gene. Researchers have also identified 30 different mutations within the PLOD1 gene itself, all of which are associated primarily with extremely fragile skin, just as with FFS.

Homozygous, affected foals are born with a variety of phenotypical manifestations, including open abdominal cavities, skin lesions, extremely thin skin, abnormal flexion of the joints, malformed spinal columns, lung problems, and intracranial hemorrhaging (Grillos, 2021). The thinness and extreme delicacy of the skin

are caused by a reduction in the number of and insufficient linkage between collagen fibers (Aurich, 2019). Collagen is an essential part of the body's connective tissues and helps give structure and strength to the skin (Metzger, et al., 2020).

High carrier frequencies combined with the low numbers of reported cases lead researchers to believe that homozygous, FFS-affected foals most commonly die during gestation. They also think that this occurs more frequently than previously reported (Grillos, 2021). FFS-caused miscarriages are likely overlooked because genetic testing is mainly done on adult horses and has yet to be included as a routine diagnostic in cases of miscarriage. A study in 2019 investigated the causes behind 52 cases of miscarriage, stillbirth, and birth of non-viable foals. Thirty-six of the cases were in Warmbloods, 13 in other breeds, and 3 in unknown breeds. Fifteen cases were suspected of being caused by FFS, while the other 37 cases were submitted without suspicion of FFS. Of the 15 suspected cases, 14 were homozygous for the FSS-causing mutation. A further 3 cases were heterozygous for the FSS mutation, while the rest of the cases were negative. All 14 of the homozygous foals were Warmbloods, while the heterozygous cases consisted of one Warmblood, one Thoroughbred, and one unrecorded breed. The 14 FFS homozygous foals miscarried between the 9^{th} and 11^{th} month of gestation, while the heterozygous and negative miscarried foals were lost anywhere between 4 and 11-months of gestation. The observed variances in physical signs of FFS within the study, from only the tail affected to extensive lesions and extreme deformations, is a likely cause for the low numbers of reported FFS cases. Cases where there are none or only a few visible abnormalities may not be investigated as to whether or not there is a genetic cause (Aurich, 2019).

Case Studies

A study published in 2020 examined a necropsy on a stillborn, FFS-affected Oldenburg filly who was born two weeks before the due date. The filly suffered from severe skin tearing and ruptured abdominal muscles that caused an opening in the abdominal cavity (see Appendix A). Researchers compared the filly's skin to two similarly-aged foals unaffected by FFS – one a Thoroughbred and the other a Warmblood. The affected filly had fewer collagen fibers in the areas affected by the worst skin ruptures and "a severely reduced" amount of collagen fibrils in all of the examined skin (Metzger, et al., 2020).

Figure 1

Oldenburg Filly affected by Fragile Foal Syndrome. Metzger, et al., 2020.

In 2021, researchers published a case study on the first Thoroughbred foal believed to be affected by FFS. The case first came to veterinary attention at 278 days gestation when the mare presented with premature mammary development. Ultrasounds revealed a subcutaneous cyst on the foal's neck that continued to grow in size as gestation continued. The mare went into labor at 309 days gestation. Veterinary assistance was required for the delivery, during which the foal suffered tearing of the skin on the forelegs. The foal was euthanized shortly after birth due to skin damage, a variety of skin lesions, and developmental deformities. A necropsy disclosed that the foal was affected by "collagen dysplasia." Researchers used whole-genome sequencing to test the foal's DNA and analyze 1,799 possible causative genes, including the known PLOD1 FFS mutation and the mutation that causes Hereditary Equine Regional Dermal Asthenia (HERDA). The results were compared to 34 control samples from over 11 different breeds. The foal tested homozygous for the PLOD1 FFS mutation and homozygous for the normal allele at the locus where the HERDA mutation is located. Two other mutations were identified as possibly affecting the function of proteins similar to PLOD1, but neither of the genes has ever been connected to phenotypical manifestations similar to FFS in any species, so researchers did not pursue any further investigation into these mutations. In light of the foal's homozygosity for the PLOD1 variant and the lack of any other likely cause for the foal's abnormalities, researchers concluded that this was the first confirmed case of Warmblood Fragile Foal Syndrome in a Thoroughbred and recommended that "Warmblood" be removed from the syndrome's name (Grillos, 2021).

The recent confirmation of a FFS-affected Thoroughbred foal and the subsequent discovery that Thoroughbreds carry the mutation has prompted researchers to explore the

idea of what other breeds might carry the mutation. A study published in 2020 tested the DNA of 7,343 horses spanning 78 different breeds. Unsurprisingly, Warmbloods had the highest carrier frequency for the allele, particularly Westphalians, with an allele frequency of 20%. Hanoverians had the second-highest carrier frequency at 17.86%, which would seem to support other research that suggested that the W/F-line in Hanoverians were the progenitors of the mutation. However, the high frequency of 16.67% in the unrelated Halflinger along with small percentages in other unrelated breeds, seem to suggest otherwise (Martin, 2020). Another study into the prevalence of the PLOD1 mutation in the equine population tested over 4,000 horses. Results found the PLOD1 mutation in 21 breeds, most of which were Warmbloods except for Thoroughbreds (1.19%), Halflingers (2.08%), American Sport Pony (4.17%), and Knabstruppers (3.26%) (Grillos, 2021).

Where did Fragile Foal Syndrome come from?

To date, researchers have not been able to identify the source of the PLOD1 mutation that causes FFS. Analyzing the pedigrees of carriers suggests that the PLOD1 mutation is most common in Hanoverians, Selle Francais, Dutch Warmbloods, Oldenburgs, and Westphalians, with one analysis identifying a Hanoverian stallion born in 1861 as a possible source (Brooks, 2021; Ablondi, 2022). However, examining pedigrees presumes that there was one common source of the FFS allele, which is improbable considering that carriers have been identified across a wide selection of breeds. Other pedigree analyses implicated the Thoroughbred stallion Dark Ronald XX, who makes an appearance in the pedigrees of a large number of sport horses (Brooks, 2021). Dark Ronald XX was imported in 1913 to stand at stud in Germany. Through his progeny, he has had a long-lasting effect on German Thoroughbreds and Warmbloods (Zhang, et al., 2020). After his death from colic in 1928, Dark Ronald XX's heart, skin, and skeleton were preserved, and later genetic testing of museum exhibits of his remains conclusively proved that he did not carry the mutation (Zhang, et al., 2020; Brooks, 2021).

The presence of the FFS allele in Thoroughbreds has given rise to the suspicion that therein lies its origins as Thoroughbreds heavily contributed to the development of various Warmblood breeds (Brooks, 2021). Analyses estimate that the Hanoverian owes approximately 34.8% of its genes to the Thoroughbred (Metzger, 2021). One theory is

that the allele might go back to the foundation of the Thoroughbred breed and the Godolphin Arabian. The absence of the allele within the modern Arabian breed is not conclusive proof that the Godolphin Arabian is not the source of the mutation, as genetic research has shown that the Godolphin Arabian does not share ancestry with the modern Arabian. Researchers and historians have come to understand that, in that time period, "Arabian" was a term applied to any horse from beyond Western Europe. The three foundation stallions of the Thoroughbred were most likely related to the ancestors of the modern Akhal-Teke and Turkemen horses (Brooks, 2021). The relatively low allele frequency of FFS within the Thoroughbred, around 1.2%, is explainable by the fact that Thoroughbred stallions used in Warmblood breeding were not used for Thoroughbred breeding because they usually had little success as racehorses and were not desirable as racehorse sires (Metzger, 2020).

Reports of lesions similar to those seen in FFS were recorded in the 19th Century in purebred Arabians within Germany that were closely inbred to the Syrian stallion Bairactar, who appears in the pedigrees of a large portion of modern European Warmbloods. These foals were born alive after a normal or close to normal gestation and suffered from lesions on the legs and back as well as flexed forelegs. Pedigree studies prove that these foals were affected by an inherited condition, but there is no way to prove that these foals actually suffered from FFS and not some other inherited disorder (Aurich, 2019).

Why is FFS becoming of such concern now?

Fragile Foal Syndrome (FFS) has been around for a while. Commercial genetic testing became available in 2013, and the first case study was peer-reviewed and published in 2015, though FFS had been appearing off-and-on in publications for years. The widespread interest and furor started in 2018 when Hilltop Farm revealed on social media that one of their stallions, Sternlicht, was a carrier. Hilltop Farm announced the stallion's carrier status and that they were removing him from their 2018 stallion roster to raise awareness about FFS.[27] Information and public interest spread so quickly because the news was disseminated on public platforms rather than in long and technical scientific publications. Responses among the equine community ranged from mild interest to outright panic (Brooks, 2021). While panic helps nothing, it would be better to be concerned now, while the problem is still small, than to wait until it severely affects the population. Scientists know that it is an autosomal recessive disorder, which is beneficial because it requires the presence of two alleles before it can be expressed. Testing conducted through breed registries will hopefully help to determine the frequency of the FFS allele in the Warmblood population. These two pieces of information will help researchers assess the impact that FFS has now and could have in the future. The frequency of stallions carrying FFS is of more concern than mares carrying the recessive

[27] *Sternlicht Withdrawn from Hilltop Farm 2018 Lineup*. (2018, April 6). Warmblood Stallions of North America. http://breeding-news.warmbloodstallionsna.com/2018/04/sternlicht-withdrawn-from-hilltop-farm.html#:~:text=Hilltop%20Farm%20has%20just%20announced%20the%20withdrawal%20of,about%20this%20situation%2C%20and%20more%20clarification%20is%20needed.

allele. A popular sire can have several times more offspring in a single breeding season than a mare will have in her entire breeding lifetime. As Impressive demonstrated in Quarter Horses, it only takes a single stallion to spread a debilitating disorder through an entire breed (Tryon, et al., 2009).

However, some breeders are relatively unconcerned by this because the confirmed incidence of homozygous foals is not as high as could be expected with the population's carrier frequency. In Hanoverians, scientists discovered a correlation between carrier status and increases in estimated breeding values for conformation and gaits. These findings are worth further study to determine if carrier status actually imparts a performance advantage or if it is simply a result of there being a higher number of carriers in dressage bloodlines (Brooks, 2021).

Could carrier-status be beneficial?

Warmblood breeding stock are selected almost exclusively based on their performance in competition. This selection favors horses with high joint mobility and elastic movement, particularly in dressage horses. Though hypermobility is classified as a disease in humans, people affected by hypermobility frequently outperform their competition in sports that require a high level of mobility. Since one of the phenotypical manifestations of FFS (FFS) in homozygous foals is extreme flexion of the joints, researchers theorize that carrying one non-lethal allele might give some horses an edge. Some research has connected the FFS allele to estimated breeding values (EBV) for traits including conformation, gaits, and others associated primarily with dressage. The researchers involved in this study examined genetic divergence between Swedish Warmbloods bred for dressage and those bred for jumping. For this study, 621 horses were evaluated on "traditional evaluating traits," including "type, correctness of legs, walk, trot, canter, temperament for gaits, jumping technique, jumping temperament, show jumping, and dressage." An additional 507 horses were evaluated using 50 "linear descriptive traits," of which 13 were jumping-related, 15 were movement-related, 21 were conformation-related, and one was behavior-related. The results seem to favor a beneficial aspect of being an FFS carrier. The results of the study showed a "significant" effect of FFS carrier status on six of the "traditional evaluating traits." These traits were walk, trot, canter, temperament for gaits, dressage ability, and showjumping ability. Dressage ability and "temperament for gaits" had the highest benefit, with FFS-carrier

horses scoring 7.46 points and 6.95 points higher than their FFS-negative counterparts. FFS carrier status proved detrimental for showjumpers, with carriers scoring 2.50 points lower than non-carriers. Nineteen of the fifty "linear descriptive traits" were affected by carrier status, both positively and negatively, though there were more positives than negatives. Negative effects included shorter croups, being over at the knee, a propensity for paddling, less scope for jumping, and poor "distance estimation" and confidence when approaching jumps. Positive effects were a longer body, neck, and loins, more arched necks, lower withers, more supple movement, more even cadence at the walk and canter, and a more elastic trot (Ablondi et al., 2022).

A connection between FFS carrier status and increased performance ability is also supported by the fact that it is not the only harmful mutation that appears to confer a competitive advantage. Although it has not been investigated, there appears to be a correlation between the mutation for Hereditary Equine Regional Dermal Asthenia (HERDA) and increased performance in cutting-bred Quarter Horses. Three of the ten leading lifetime sires of cutting horses are carriers of HERDA and have combined lifetime earnings of $109,008, 304, which is 42% of the total lifetime earnings of the ten top sires. The average winnings for one of the carrier sires' offspring is $31,583. The seven non-carrier top ten stallions have combined earnings of $152,148,156, and each of their competitive offspring averages $27,429 in winnings. Further analysis of the earnings of the top carrier vs. top non-carrier stallions shows that, since 1998, the earnings of top carrier stallions have been increasing at a rate of roughly 5% faster than the earnings of non-carrier stallions (Rashmir-Raven, 2013).

Can Fragile Foal Syndrome be eliminated?

While more studies need to be done on the subject, the research by Ablondi et al. strongly suggests a correlation between FFS carrier status and increased dressage ability in Swedish Warmbloods. If further studies confirm this in other Warmblood breeds, this could present a problem to those who want to work to eliminate the mutation. Since breeding stock are selected from the most successful individuals, an increase in the number of successful carriers could lead to an increase in the overall number of carrier individuals.

Completely eliminating the FFS allele from the population might not even be possible. Since stallions produce so many offspring per breeding season, the onus for eliminating FFS would rest mainly on the owners of carrier stallions. Ablondi et al. conducted a simulated breeding program to examine this question. The results indicated that significantly reducing, if not totally eliminating, the carrier frequency of FFS might not be so tall of an order after all. In fact, significantly reducing the frequency might not even require eliminating every carrier stallion from the gene pool. In these simulations, removing every carrier stallion from breeding consideration decreased the carrier frequency to less than 1% in only four generations. The study also ran simulations of two more groups of stallions in the Top 10 and Top 100 Estimated Breeding Values (EBV) for dressage and showjumping. Allowing carriers in the Top 10 for the breeding goal to breed produced the same result as eliminating carrier stallions. The frequency still

decreased to around 1% by the fourth generation. Allowing carrier stallions anywhere in the Top 100 to be used for breeding resulted in a much slower rate of decrease in the number of carriers and a total carrier frequency of 8-9% (Ablondi, et al., 2022).

Analysis

It is doubtful that inbreeding will ever cease to be a source of concern and debilitating disorders in the equine world. In the roughly 200 years since the formation of studbooks and the consequent intensification of inbreeding for desirable traits, genetic heterozygosity has decreased by 16%, and the number of hereditary genetic mutations has increased by around 4% in the equine population (Fages, et al., 2019). Modern developments in equine reproduction, such as cryopreservation, semen extenders, and overnight shipping, give breeders access to the most popular and successful stallions around the globe. Now, access to stallions is not limited by geography but only by how many mares he can service and how many breeders are willing to pay his stud fees.

Warmbloods are particularly prone to decreasing genetic variation and consequent mutation spread since they are a “type” rather than separate breeds. Both mares and stallions can be approved by registries other than the one they were born into. Stallions can even be approved by multiple registries. A successful and sought-after stallion, approved by multiple registries, contributes to decreasing genetic variation the more foals he produces across more “breeds.”

One way to try to stabilize decreasing genetic diversity would be to place a limit on the number of mares each stallion can breed each year. This method has actually been tested in both Thoroughbreds and Standardbreds, with varying degrees of success. The Jockey Club implemented a cap of 140 mares per stallion, per calendar year in May of

2020, which would affect all stallions foaled in or after 2020. The rule was rescinded in February of 2022 after a lawsuit was filed by three of the biggest stud farms in Kentucky, and further backlash that reached all the way to the Kentucky legislature.[28] Walker Hancock, the president of Claiborne Farm, expressed his disappointment over the Jockey Club's decision and worry over the seeming lack of attention to the underlying issue of decreasing genetic diversity. "I'm not sure of the next step, but we are still left with the problem the Jockey Club attempted to alleviate, which is that there is a serious concern for the narrowing genetic diversity of the breed. I think it's worthy to continue to have an open conversation with all stakeholders on how we go about fixing this issue, which might not be serious currently, but will be a dire problem 20-plus years into the future if nothing changes."[29] Statistical data appears to support Walker Hancock's concerns about impending problems if the issue of genetic diversity remains unresolved. Since 2007, the number of stallions with books of more than 140 mares increased from 37 to 43 in a total stallion population that has been decreasing over the same number of years. A study conducted in 2011 by Drs. Matthew Binns and Ernie Bailey found a "marked increase" in the amount of inbreeding in books of 100 or more mares. The 2021 Report of Mares Bred for North America shows that of the Top 16 stallions with the most mares bred, seven of them were closely related to each other. These seven were Into Mischief, five of his sons, and his half-brother, Mendelssohn. Four of these seven bred over 200 mares, while the other three bred 190, 189, and 197 mares.

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[28] Mitchell, E. (2022, February 15). *KY Bill Takes Aim at Jockey Club Stallion Cap*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/256838/ky-bill-takes-aim-at-jockey-club-stallion-cap

[29] Mitchell, E. (2022, February 23). *Mare Cap Rule Shelved, But Inbreeding Still a Concern*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/257011/mare-cap-rule-shelved-but-inbreeding-still-a-concern

The Standardbred industry also instituted a mare limit due to genetic concerns. The United States Trotting Association (USTA) asked Dr. Gus Cothran at the University of Kentucky's Gluck Equine Research Center to perform an analysis of heterozygosity within the Standardbred. Dr. Cothran's research showed that there was indeed a trend of decreasing genetic diversity, and in 2009, the USTA enacted a 140-mare limit. A genetic study to see the impact of this rule is still being conducted, and results are not yet available. Standardbreds differ from Thoroughbreds in that artificial insemination is permitted, and some breeders believe that, together, the use of AI and the mare cap will ultimately benefit the breed. Bob Brady, who co-owns the 2021 Standardbred Horse of the Year, says, "We were backing ourselves into a corner. I think the cap has opened some avenues for other stallions to get a chance at stud. We also have an influx of semen from Europe, which will greatly expand our genetic base, so I think the goal has been achieved. We know the mare cap was a move in the right direction, and it's basically had little impact on our operation."[30]

Just because this information mainly concerns Thoroughbreds and Standardbreds does not mean it does not apply to Warmbloods. While Warmbloods may not be at the same level of lack of genetic diversity as Thoroughbreds, it would be better to do something about it now, rather than wait until it actually is a problem. Similarly, even though only a few warmblood foals have been born affected by FFS, the carrier frequency indicates higher effects than most know. A mare cap for warmbloods would serve a double purpose. It would help slow the decrease of genetic variation and help to

[30] Mitchell, E. (2022, February 23). *Mare Cap Rule Shelved, But Inbreeding Still a Concern*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/257011/mare-cap-rule-shelved-but-inbreeding-still-a-concern

stem the spread of FFS. The majority of breeders are ethical and avoid breeding horses that are too closely related or that both carry lethal mutations. However, there always have been and will be those who are willing to do anything to make a buck and who are willing to take a chance and play the genetic lottery.

One of the articles dealing with the Jockey Club's mare cap brought up several potential issues with the cap that could have serious economic ramifications. Though the article brings up these issues only as they apply to Thoroughbreds, they could also apply to warmbloods. The first issue is that if mare owners are not able to breed to the top stallions that they want to, they may not breed their mares at all, rather than sending them to lower quality stallions. This, in turn, would result in fewer foals and horses entering the sales market.[31] A representative of Keeneland worried that their yearling sales would suffer a steep decrease in revenue due to fewer foals by highly desirable, leading sires such as Into Mischief.[32] Other industry people believe that a mare cap would drive quality stallion prospects overseas to countries with no mare cap in place.[33]

The benefits of Fragile Foal Syndrome (FFS) carrier status still need more research to determine the exact scope, if any, of these benefits. Still, the current research appears to support the theory. If further research does indeed conclude that FFS carrier status confers a competitive advantage to dressage horses, it raises a host of questions

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[31] Mitchell, E. (2022, February 17). *Breeders React to Jockey Club Mare Cap Rule Rescission*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/256873/breeders-react-to-jockey-club-mare-cap-rule-rescission

[32] Mitchell, E. (2022, February 17). *Breeders React to Jockey Club Mare Cap Rule Rescission*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/256873/breeders-react-to-jockey-club-mare-cap-rule-rescission

[33] Mitchell, E. (2022, February 23). *Mare Cap Rule Shelved, But Inbreeding Still a Concern*. BloodHorse. https://www.bloodhorse.com/horse-racing/articles/257011/mare-cap-rule-shelved-but-inbreeding-still-a-concern

about ethics – regarding both the horses and the show circuit. Purposefully breeding for carrier status would cause a drastic decrease in the number of successful horses without the mutation. A case in point is the similar disease Hereditary Equine Regional Dermal Asthenia (HERDA) in Quarter Horses. “Patient zero” was intensely popular in cutting horse lines, and within 30 years, a third of the entire cutting-bred population were carriers (Heineking-Schutte, 2018). If the most successful mares and stallions were all carriers, this could lead to matings between carriers. Responsible breeders have a passion for their chosen breed or discipline and value the welfare of their animals above profits. These breeders would not risk the chance of breeding an affected foal, even though the odds for mating between two carriers favor getting a carrier foal that is not adversely affected. However, there have always been and likely will always be people willing to play the odds in a quest for a more competitive and profitable horse.

Since MSU has a warmblood broodmare, it is important that the university consider how issues in the warmblood world might affect them and their equine program. Murray State University’s warmblood broodmare, Lady Carthago (Lady), is an excellent example of how Warmbloods can get their genetics from, and pass them on to, multiple warmblood “breeds.” While approved by the Oldenburg registry, Lady is by pedigree a Holsteiner. Lady’s most recent foal, River, is registered as an Oldenburg but by pedigree, is a combination of Holsteiner, Westphalian, Thoroughbred, Dutch Warmblood, Selle Francais, and Hanoverian registered horses. There is even an Anglo Arabian about five generations back on her sire’s side. As a consequence of this common conglomeration of types, breeders need to consider not only the effect that FFS could have on the foal but also the effect that being a carrier could have on the multiple “breeds” to which that foal

may one day contribute its genes. This is one of factors that MSU has to take into consideration for their breeding program. Being a public institution, MSU also has to keep in mind public perception. Lady has never been tested to see whether or not she is a carrier for FFS, so it is conceivable that she could be bred to an untested carrier stallion and produce an affected foal. If she did produce an affected foal, MSU would have two options. One option would be to publicly announce the birth and subsequent euthanization of an affected foal and confront any backlash head-on. The second option would be to try to avoid any unpleasantness by not announcing the birth of an affected foal and hoping the fact will quietly fade into history.

Ideally, Lady would be tested before any future breeding to entirely avoid the possibility of an affected foal. This would be the safest course to avoid any backlash and unfavorable public opinion. Animal Genetics offers a test for FFS for $40 plus the cost of postage to send in the hair sample.[34] However, because Lady is twenty-three years old and likely will not be having too many more foals, even via embryo transfer, testing her is not as imperative since breeding her to a tested clear stallion will prevent the possibility of an affected foal.

Were Lady or any future warmblood broodmare at MSU to have an affected foal, the best course of action would be to proactively announce the fact to the public. Doubtless there will be backlash from animal rights activists and even possibly from other members of the public who are not well informed about livestock animals, but this course of action places MSU in the best light. Not announcing the fact makes it look as if

[34] *Warmblood Fragile Foal Syndrome (WFFS).* (n.d.). Animal Genetics. https://www.animalgenetics.us/Equine/Genetic_Disease/WFFS.asp

MSU has something to hide and would give some credence to any suggestions of negligence or malfeasance on the university's part. Making a public announcement gives MSU the opportunity to appear upfront and honest and to push for more research on FFS. This was Hilltop Farm's approach when they announced that Sternlicht was a carrier, and they were removing him from that year's stallion roster. Their announcement was favorably received with commenters mentioning their integrity and admiring their transparency. [35]

Another factor that MSU has to take into consideration is the expense of raising a foal. The primary purpose of MSU's breeding program is generate additional income for the school's equine program. A foal affected by FFS would deprive MSU of this additional yearly income. A bad reputation gained from not making the birth of an affected foal public could also make it harder for MSU to sell future foals. During the last seven years, Lady's foals have brought in an average of $5,000. The 2019-2020 breeding season resulted in a colt that sold for $5,000. As shown in the table on the next page, total expenses were $4,626.50. This season's expenses were high because the foal required hospitalization and treatment, leaving profit of only $373.50.

[35] *Sternlicht Withdrawn from Hilltop Farm 2018 Lineup*. (2018, April 6). Warmblood Stallions of North America. http://breeding-news.warmbloodstallionsna.com/2018/04/sternlicht-withdrawn-from-hilltop-farm.html#:~:text=Hilltop%20Farm%20has%20just%20announced%20the%20withdrawal%20of,about%20this%20situation%2C%20and%20more%20clarification%20is%20needed.

Table 1

Murray State University Breeding Expenses for Lady Carthago – 2019-2020.

Expenditure	Cost
Farrier	$750
Feed & Hay	$1,480.50
Ultrasounds	$590
Medications	$264
Tests	$110
Procedures	$321
Artificial Insemination	$135
MSU Farm Visit	$105
Hospitalization	$210
Foal Treatment & Medications	$661
Total Cost	$4,626.50

The 2020-2021 breeding season was much more successful than the 2019-2020 season. An entirely uncomplicated pregnancy resulted in a filly that was the first of all the warmblood foals bred at MSU to be awarded Premium at the Oldenburg foal inspection. The Premium designation on the filly's registration garnered a selling price of $6,000, leaving MSU with a profit of $3,158.50.

Table 2

Murray State University Breeding Expenses for Lady Carthago - 2020-2021.

Expenditure	**Cost**
Farrier	$750
Feed & Hay	$1,480.50
Ultrasounds	$260
Medications	$134
Tests	$0
Procedures	$57
Artificial Insemination	$70
MSU Farm Visits	$0
Hospitalization	$90
Total Cost	$2,841.50

As a public institution, MSU has to find a happy medium between animal welfare and looking out for their own interests in the monetary and public relations spheres. While perhaps not a significant part of the yearly budget, the yearly income from a warmblood foal does contribute to the equine program's ability to improve its facilities and program. A miscarried foal or a foal lost to FFS would cost money, as would the negative public relations image that could come from hiding Lady's genetic flaw. This monetary loss could reach into the several thousands. Ethically, the best course of action if an FFS affected foal were born would be to announce the fact and to take steps to ensure it does not happen in the future. This would also be the best option from a public relations point of view. This option allows the university to present it as the tragic loss of the genetic lottery that it is.

The ramifications of FFS also involve current and future advances in reproductive manipulation. Humanity has already developed a multitude of ways to alter the reproductive process from what nature created. These and any future developments could change how we deal with harmful mutations. Gene editing proved to be successful in producing Genetically Modified Organisms (GMOs) in plants. While it is not yet commonplace in animals, it is not too farfetched to imagine it will soon become common. It would eliminate the worry of breeding an affected foal by crossing two carriers. If the embryo was affected, its genes could be edited to normal or carrier status, as the breeder desired. Intracytoplasmic Sperm Injection (ICSI) could also be a useful tool for a breeder who wants to cross two highly successful and complementary horses that were carriers. ICSI only requires a single sperm, so if the oocyte contains the mutation, the laboratory

would only need to pick a sperm from the desired stallion that does not carry the mutated gene (Salamone, et al., 2017).

As with most technological advances, there are potential downsides, ethical conundrums, and potential benefits. If breeders no longer have to worry much, or at all, about the impact of their breeding practices, it could lead to an increase in the number of harmful mutations within the population. Commonplace genetic manipulation would allow breeders to purposefully breed for harmful, carrier beneficial mutations and edit any affected foals to non-lethal carrier status.

Though debates over future possibilities are good, speculation about the future is just that, and there is no guarantee it will happen. The old saying, "An ounce of prevention is worth a pound of cure," is still as pertinent now as whenever it was first coined. Ethical breeders are not willing to trade the welfare of their horses or an entire breed for a competitive advantage, and breed registries, as well as other interested entities, are already taking steps to prevent the spread of FFS. Germany has an animal welfare act that "prohibits mating of two vertebrates when they are at risk to produce deficient offspring that will suffer" (Heineking-Schutte, 2018). Researchers believe that the majority of FFS-affected foals miscarry at some point during gestation, but it is inarguable that those that do survive to birth suffer in their short lives. The Royal Dutch Warmblood Association of North America (KWPN-NA) is one of the breed registries that now require all registered stallions and stallion prospects to be tested. KWPN-NA had been recommending voluntary testing for some time but made it official in May of 2018 after three stallions tested positive. This mandate required owners to test all actively breeding stallions and all stallions taking their performance tests. Once tests results are

received, they are publicly available on KWPN-NA's website.[36] In the wake of changes to the European Union's animal welfare regulations in 2018 that made testing for "genetic defects" mandatory, the German Equestrian Federation made a similar ruling. As of the 2019 breeding season, all Warmblood registries in Germany will have to make testing results for all registered horses publicly available on their websites (Eurodressage, 2018).

If carrier frequency continues to climb, a possible future option for registries would be to disallow the registration and granting of breeding licenses to some or all mares and stallions that carry FFS. Banning all carriers, both mares, and stallions, from reproducing would likely be too extreme, but only preventing a select number of carrier stallions from reproducing would still be highly beneficial. A recent study conducted theoretical breeding projections. Study results showed that allowing carrier stallions in the top 10 of estimated breeding values for desired traits to reproduce saw the carrier frequency decreasing to under 1% in four generations (Ablondi, et al., 2022).

[36] Keeler, J. (2018, May 10). *New Policy for Stallions regarding Warmbloods Fragile Foal Syndrome (WFFS)*. KWPN North America. https://kwpn-na.org/about/new-policy-for-stallions-regarding-warmblood-fragile-foal-syndrome-wffs/

Summary

Domestication has had and continues to have cumulative effects on the equine population. Reproductive selection by humans rather than natural selection does increase desirable traits, but it has the side effect of accumulating harmful traits. In addition, the levels of inbreeding decrease the genetic variation within a breed population, allowing for the rise and spread of mutations such as FFS (Bailey, 2015; Orlando & Librado, 2019). Other strategies to reduce inbreeding exist, with varying levels of difficulty and success, but the surest way is to avoid mating closely related horses. Ideally, these horses would not be related at all, but there should be at least several generations between a common ancestor. Thoroughbreds are a perfect example, with faster speed coming hand-in-hand with soundness issues (Hedrick & Garcia-Dorado, 2016; Todd, et al., 2018).

Fragile Foal Syndrome is not the only recessive genetic disorder affecting the skin and connective tissues. Hereditary Equine Regional Dermal Asthenia (HERDA) and Junctional Epidermolysis Bullosa (JEB) have been of serious concern within the Quarter Horse and Draft breeds for over three and the last two decades, respectively (Rashmir-Raven, 2013; Capelli, 2015). It is high time that FFS received serious public interest and scientific research to prevent further harm to the equine industry and equine welfare. The case studies discussed highlight both. Every foal loss is a hit to the equine economy, particularly for small breeders who may depend on a couple of quality foals per year to keep their operation afloat. Foals that survive till birth are born with severe structural

malformations and injuries. One can only imagine how painful their short lives must be before they are euthanized (Grillos, 2019).

Though researchers have not yet been able to narrow down FFS's origins, studies are still ongoing. Pedigree analysis remains inconclusive, and a single progenitor is improbable. The Thoroughbred origin theory remains the strongest since they contributed so heavily to the formation of the warmblood types (Brooks, 2021).

Investigation into the possible benefits of FFS carrier status remains in its infancy, though current information suggests a correlation (Ablondi, et al., 2022). Regardless of whether or not a correlation is established, temporary benefits cannot outweigh the continued loss of genetic variation and the spread of a harmful mutation. Theoretical ways to reduce the carrier frequency of FFS are promising but not yet conclusive. Ablondi et al. believe that it is possible to reduce the carrier frequency to 1% or less within four generations through judicious issuing of stallion breeding licenses (Ablondi, et al., 2022). Regardless of this idea's success, or lack thereof, continued efforts must be made to find a way or ways to reduce the threat.

Future advances in artificial reproductive techniques and technology could offer breeders freedom from worry about genetic abnormalities and lack of genetic variation by giving them the ability to have their foal's genes edited to avoid any problems. While these advances may come bearing benefits, they would also come bearing ethical issues. When it comes to ethical issues, it is always an excellent idea to err on the side of caution. Just because you can do something does not mean you should. Genetic mutations arose due to human interference in a natural process. Therefore, it is the responsibility of humans to minimize the chance of new mutations arising and to decrease the spread of

mutations that already exist. This applies to FFS. Thankfully, many breeders and warmblood registries recognize that potential benefits do not outweigh the possibility of irreparable harm to the genetic integrity of warmblood breeds. With continued public knowledge and education about FFS and advocacy for animal welfare and genetic preservation, perhaps one day, we might see FFS eliminated from the equine population.

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