Genetic health conditions in USA Fjords and considerations for breeding

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Fjord owners and those new to the breed frequently ask if there are any known genetic health conditions to watch for in Fjords. The answer most often given is that the Fjord is a healthy breed without the issues commonly found in other horse breeds, such as HYPP, PSSM1, GBED, HERDA, MH and others. As genetic investigation has improved over the years, new mutations and variants have been identified that correlate with expression of some equine health conditions, and thus we now have improved tools for detecting these conditions before they are expressed, and for making smart breeding decisions by knowing the carrier status of unaffected horses. A research project currently underway in Norway, the FeNomen Project, is requesting hair samples from Fjord stallions that have offspring in Norway, to test for the prevalence of the IAR genetic subfertility variants that have been identified in the Fjord breed and could be contributing to the acknowledged low mare pregnancy rates in Fjords in Norway and other countries. This got me wondering if there are other such health conditions that aren't well known or publicized in the Fjord breed. If we know what conditions exist in Fjords, we can use that knowledge to further improve the health of Fjords and reduce the cost of ownership by breeding more individuals that are genetically healthy.

I contacted Etalon Diagnostics, a company that is on the forefront of equine genetic health discovery and research, that specializes in providing individual genetic health assessments for horses, and conducting research to further improve equine genetic knowledge and health. I asked for a summary of the health conditions that the company has identified among the horse samples submitted with a breed identified as Fjord. Etalon Diagnostics is committed to confidentiality and will never share information about a specific horse or individual without express written permission of the owner, so all of the information shared is not identifiable to horse or owner. Among the 59 Fjords that have been submitted to Etalon Diagnostics for testing, there were between 55-59 samples that sequenced cleanly and the following genetic health variants were identified: IAR (impaired acrosomal reaction) also called genetic subfertility, susceptibility to ERU (equine recurrent uveitis), ERU severity risk (ERUS), EMS (equine metabolic syndrome), WNV (West Nile virus risk), lordosis risk, and RLN (recurrent laryngeal neuropathy risk) also known as roaring. The percent of tested horses that had at least one copy of the variants for these conditions are listed in Table 1 below.

Our awesome NFHR Registrar, Jeanne Poirier, ran a database count of registered Fjords that are 30 years old or younger, and that haven't been reported as deceased. That gives us a working population estimate of 6006 Fjords in the USA. If we assume that the sampled genetic condition allele frequencies are representative of the population, Table 1 shows the potential number of registered Fjords that could be carrying at least one copy of each of these health condition variants.

Table 1. Potential number of NFHR Fjords in the living population with at least 1 copy of these variants

Genetic Variant	Percent[1]	Count[2]
Lordosis Risk	90%	5395
Subfertility, IAR Risk, Variant 1	68%	4076
Subfertility, IAR Risk, Variant 2	50%	3003
Equine Metabolic Syndrome Risk	39%	2341
Equine Recurrent Uveitis Risk	32%	1934
West Nile Virus Susceptibility	27%	1629
Recurrent Laryngeal Neuropathy Risk	2%	102
Equine Recurrent Uveitis Severity Risk	2%	102

[1] Percent of Etalon Diagnostics Fjord samples

[2] Count of living NFHR Fjords that could be carriers

Etalon Diagnostics (https://www.etalondx.com/horse-health-and-disease-genes) has a very informative website, detailing the known inheritance patterns for these health conditions, the degree of confidence that research to date has for predicting a result of the genetic test, and how to interpret a positive result. The Merck Veterinary Manual online (https://www.merckvetmanual.com/horse-owners) contains even more details about diagnosis of symptoms and management of health conditions. Each Fjord owner's veterinary team is also a great resource for treatment and management strategies.

This article contains terms that are defined as follows: a variant is a loci, or location in the genome, with a mutation. Each Fjord has 2 alleles at that loci. One allele is inherited from each parent, and based on what the parents carry, the offspring could inherit normal or variant alleles. Each loci typically has three options for its genetic status: negative or clear is two normal alleles (n/n), heterozygous is one normal and one mutated allele (n/mutation), and homozygous is two mutated alleles (mutation/mutation). If both parents are n/n, then all offspring will inherit n/n at that loci; both

unaffected and not a carrier. A Fjord that is heterozygous is a carrier and thus has a 50% chance of passing the mutated allele to its offspring. A homozygous Fjord will always pass one copy of the mutation to its offspring. Since all of these conditions are risks, not guarantees, a homozygous Fjord may not be affected by the condition.

In the following paragraphs, I describe in greater detail the health conditions found in this set of 55-59 Fjord samples.

The subfertility gene (IAR, impaired acrosomal reaction) that the Norwegians are assessing in their Fjords contains 2 variants that can result in reduced sperm functionality and thus fewer or later bred mares for stallions that are homozygous for both variants. Within this set of Fjord samples, 32% were negative (n/n) for the Variant 1 (V1) mutation and 50% were negative for Variant 2 (V2). 48% were heterozygous for the V1 mutation, and 47% for V2. 20% were homozygous (IAR/IAR) for V1 and 3% for V2. There is no known fertility implication for carriers of 1, 2 or 3 IAR mutations. None of the tested Fjords were homozygous for both variants (IAR/IAR, IAR/IAR), which is correlated with subfertility but about 81% had at least one allele of both variants. Mares are not affected but can produce affected colts if they pass the variants along to their offspring.

The risk for Equine Metabolic Syndrome (EMS) and its associated laminitis risk is increased 9 times in Arabians that are homozygous for the mutant allele at gene FAM174A. Fjords in the Etalon Diagnostics database show 61% as clear, 37% as carriers and 2% as homozygous for the mutation that is correlated with the increase in EMS and laminitis risk in Arabians. Diet and exercise are effective management strategies for this genetic predisposition. It is also possible to breed for individuals that do not have this particular genetic variant, but there are hundreds of other genes that contribute to EMS, and we don't have enough Fjord samples to know which are the most impactful on expression of this condition in our breed, so knowing the FAM174A status of our Fjords is useful, but not the whole picture for avoiding this condition.

The West Nile Virus (WNV) susceptibility gene variant has been correlated with an increase in the symptom susceptibility risk to WNV, if your Fjord contracts the virus. A clear horse has the lowest risk of severe symptoms, a carrier has a higher risk and has a 50% chance of passing that variant to offspring, and a horse with 2 copies has the greatest risk of severe symptoms with a 100% chance of passing one variant allele to offspring. This information can be used by a Fjord owner or breeder, in consultation with your veterinarian, to inform how often to vaccinate the horse against WNV and potential inheritance outcomes for foals. Among the Fjords in the Etalon Diagnostics database, 73% were clear, 27% were carriers and 0% were homozygous for the variant allele, and since we don't have further data, we don't know if this gene variant affects Fjords in the same way that it does for the reference population in the study.

Susceptibility to Equine Recurrent Uveitis (ERU) is increased 5 times for carriers of the ECA20 variant, and there is an 80% increased risk with two copies of the variant allele in the reference horse population. With multiple causes, ERU may originate from environmental factors, ocular infection with *Leptospira*, a genetic predisposition or a combination of these factors, so even horses with 2 copies of the variant may not be affected if conditions are managed through exposure, vaccination, or other means. Among the Fjords in the Etalon Diagnostics database, 68% were clear, 29% were carriers and 3% were homozygous for the variant allele. There is also a separate variant within the MHC region of the genome, which encompasses genes regulating immune response, and that is correlated with a 69%-78% increased severity of uveitis in horses that have two copies of that variant. One copy is simply a carrier and was detected in 2% of the Fjord samples, with 98% testing clear.

Susceptibility to lordosis at a young age in Saddlebreds is associated with mutations in 4 regions of gene ECA20. Although this hasn't been demonstrated in other breeds, Fjords in this dataset do have mutations in all 4 of the variant regions for this condition. Saddlebreds homozygous for mutations at all 4 regions had an 80% likelihood of being affected by lordosis, and 23% of swayback Saddlebreds were heterozygous at all 4 regions. Among Fjords in the Etalon Diagnostics database, 8% were free of allele mutations for lordosis, 90% had at least one allele, 53% had two or fewer alleles, and 46% had 3 or more alleles. No Fjords carried all 8 mutated alleles in this data set.

Roaring, or the recurrent laryngeal neuropathy (RLN)-associated mutation, is a condition that results in loss of the neurons that open the larynx. Typically, the left side of the larynx is affected and restricts air flow during intense exercise. This condition develops with age, so a genetic marker is useful in identifying potentially susceptible horses early in life and for breeding animals. Geldings are more affected than mares and stallions. RLN was identified as carried in 2% of the tested Fjords (RLN/n). None were homozygous normal or homozygous for RLN. In the reference population, RLN/n was correlated with a 5 times higher risk of developing roaring than in the study population horses that were not carriers. Horses that are homozygous for this gene variant have shown about a 12 times higher risk for developing RLN than normal horses. The RLN genomic site is closely associated with LCORL, which is attributed to explaining a large portion (83.5%) of the variation that predicts taller horses, and the same 2% of RLN/n Fjords in this data set were heterozygous for extra

height (LCORL/n). Homozygotes (LCORL/LCORL) average 2.9 inches taller than horses without that gene variant.

As discussion points, none of the genetic variants identified have Fjord-specific studies published, effects quantified in Fjords, nor have any of these conditions been identified as a widespread problem among Fjords in the USA, other than perhaps EMS. Some of the Fjord-labeled samples in the Etalon Diagnostics database may not be pure or registered Fjords, with 2 of the 59 being suspect, so some of the results above could be influenced by other breeds and thus not be a relevant to the population of registered Fjords. This same investigation would need to be conducted on known registered Fjords to remove that potential. The research basis for these variants has support from investigation in other horse breeds, so it's reasonable to predict that registered Fjords could experience similar effects with these genetic variants.

The recent research in Australian ponies with EMS (2020) shows that the EMS genetic indicators for Arabians may be insufficient to inform genetic selection against this condition in native breed ponies. Additionally, Dr. Molly McCue's research at the University of Minnesota's Equine Genetics and Genomics Lab, has shown that EMS may be impacted by a few hundred different genes (2022), and thus strict breeding selection for individuals that have none of those variants would be detrimental to genetic diversity in any breed; we cannot select our way out of EMS given the vastly polygenic nature of the condition.

Some of the conditions identified in these Fjord samples can be managed with diet, exercise, or other husbandry measures, such as EMS. Some conditions, like ERU and WNV, have a vaccine against one known source, variant status simply denotes an increased susceptibility to the health condition, and if an individual is known to be genetically susceptible, the owner can manage in a way to reduce susceptibility or exposure, can be looking for symptoms and if symptomatic, and can manage the Fjord for the best quality of life.

Some conditions such as lordosis and IAR-subfertility are not symptomatic with a simple single mutation, and require two alleles of multiple variants to result in a potentially affected status, so knowledge of the carrier status of breeding Fjords can help breeders choose pairings that will reduce the chance of producing a potentially affected offspring, if those conditions express in Fjords as they do in the reference population for this article. In this set of Fjord samples, we don't have any known homozygotes for all 4 lordosis variants, so we don't know if those Fjords have swayback early in life like Saddlebreds. We also don't have any homozygotes for the two IAR variants to gain insight on fertility reduction in Fjords.

It's important to note that simply being a carrier, or positive for an increase in susceptibility, as with RLN, should not remove a Fjord from the breeding population if the horse otherwise has good qualities or an uncommon lineage to contribute to the future population. Carriers can produce clear offspring, and this is a realistic goal for Fjord breeders interested in also reducing loss of genetic diversity in the breed. Carrier individuals, or homozygous individuals for conditions that only increase risk may never experience the effect of the condition if the Fjord is managed appropriately.

Additionally, the genetic health conditions that have been identified by Etalon Diagnostics in Fjord hair samples are not as problematic as some of the serious genetic health conditions in other breeds of horses. Genetic conditions that were not identified in this sample of 55-59 Fjords includes polysaccharide storage myopathy type 1 (PSSM1), hyperkalemic partial paralysis (HYPP), glycogen branching enzyme deficiency (GBED), hereditary equine regional dermal asthenia (HERDA), malignant hyperthermia (MH), junctional epidermolysa bullosis (JEB1, JEB2), fragile foal syndrome (FFS), myotonia, hydrocephalus, androgen insensitivity syndrome (AIS), foal immunodeficiency syndrome (FIS), severe combined immunodeficiency (SCID), immune-mediated myositis, cerebellar abiotrophy, congenital stationary night blindness (CSNB) and hoof wall separation disease (HWSD). The Norwegian and Swedish Fjord breeders have been looking hard to find a genetic source for sweet itch, since there seems to be a genetic component in horses born in Norway and moved to warmer and wetter climates, but no such correlated variant has been found to date.

In summary, embracing new discoveries and technologies such as genetic health testing can help Fjord owners and breeders improve the long-term health and viability of the Fjord breed, preserve or reduce the loss of genetic diversity, improve the quality of life of current horses and those to be produced in the future, and save owners money through greater knowledge about the health conditions their horse could express and by being prepared to prevent and/or manage symptomatic conditions. All of the gene variants discussed above simply increase the likelihood of a Fjord being affected by that condition; none guarantee that the horse will be affected even if they are homozygous for the variant. We must understand the inheritance and risks associated with the various conditions, manage the environmental factors and make breeding selections that are realistic for the genetic diversity preservation or minimization of diversity loss in Fjords while promoting production of naturally healthy horses. This article is not intended to create worry or fuel witch-hunts and I encourage all owners, buyers and breeders to use this information rationally, test their Fjords, and act with

genuine kindness for our fellow Fjord lovers now and as more data are collected over time.

A huge thank you to Etalon Diagnostics for compiling and sharing the Fjord-specific genomic data and much of the condition-specific findings for this article!

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