Discovery of Deleterious Genetic Variants in Farmed Animals

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Abstract:

Data and samples are often siloed at the diagnostic labs where they are generated and collected, respectively. In this project we aim to provide an integrative service to genetically characterize samples and couple these data with their respective pathology reports to identify and publish putative deleterious alleles found in farmed animals. This project has linked scientists from 5 different research institutions, and 4 different veterinary diagnostic labs. The tools and service we have created will provide an interface that will allow diagnosticians to submit samples and reports for genetic analysis, and subsequent distribution of derived information to producers, and the research community.

Recessive lethal alleles exist benignly in breeding populations, until a sire and dam carrying them are mated. One quarter of the resulting pregnancies will be homozygous for the lethal allele and will result in an aborted pregnancy, or death soon after birth. In cattle, sheep, and horses, abortions are often necropsied. Although many have a known cause, such as being the result of a viral or bacterial infection, many do not. Those that do not may harbor a homozygous genotype for a lethal recessive allele. We currently have and are building sequence datasets for on the order of 100 healthy animals from each of these species. This project is collecting pathology reports for and will sequence 40 abortions, up to 15 each from cattle, sheep, and horses to look for alleles that are homozygous in these samples, but not in the larger population.

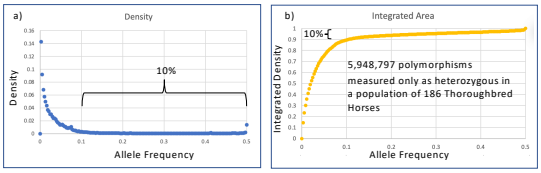
Here we present preliminary sequencing results, and methods we have developed to distinguish potential lethal alleles from variants whose genotypes have no homozygous variant genotypes due to collapsed duplications or other assembly artifacts.

Rationale:

Genetic variants that occur in a population as heterozygotes but never as homozygotes are consistent with the genetic signature of lethal recessive alleles

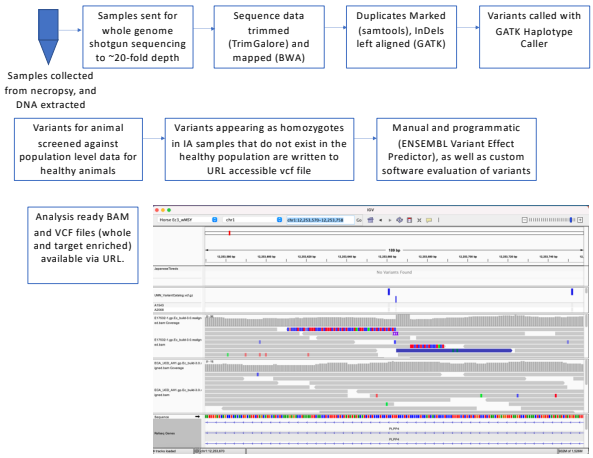
Most are simply assembly/mapping artifacts, or otherwise statistical anomalies.

By sequencing idiopathic abortions, we may identify alleles that, as homozygotes prevent development and healthy birth.



a) Allele frequency density of variants that appear with only heterozygous genotypes in a population of 5,948,797 healthy, adult Thoroughbred horses. b) The integrated area under the curve in a) showing that roughly 10% of the variants have an allele frequency greater than or equal to 10%, at which point Hardy-Weinberg calculations suggest that 1% of the population should be homozygous.

Methods:

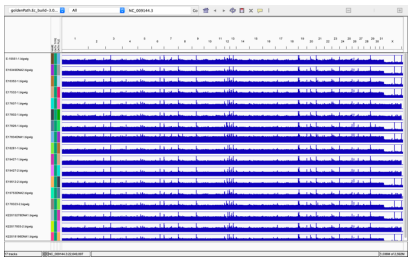


Results:

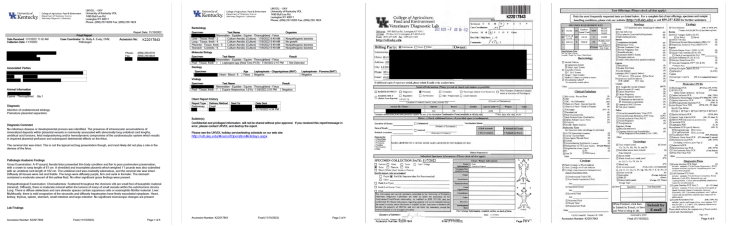
Inbreeding Analysis

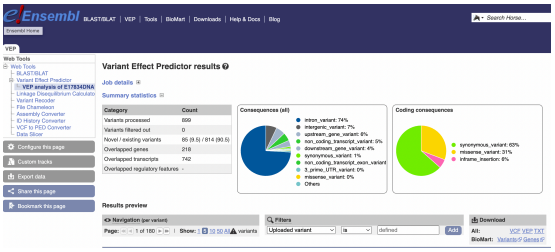
Animal	F
E-15551-1	0.318998
E16349DNA2	0.313206
E16352-1	0.328471
E17532-1	0.332093
E17607-1	0.34469
E17802-1	0.339507
E17826-1	0.292496
E178323-2	0.22322
E17834DNA1	0.30477
E18281-1	0.325326
E19427-1	0.315866
E19427-2	0.316225
E19512-2	0.306187
E19753DNA2	0.312752
K22015278DNA1	0.306462
K22017803-2	0.337567
K22018196DNA1	0.314953
Tbreds born after 2000	0.321

Coverage Analysis to identify Aneuploidys



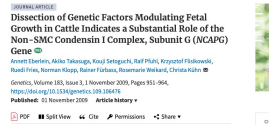
Pathology reports:





Cohort study: Haplotypes enriched in idiopathic abortions relative to the healthy population

5 out of 16 Idiopathic abortions homozygous for haplotype with 16% MAF. In a healthy Thoroughbred Population, 3 homozygotes out of 331 animals were measured when 8.7 were expected. This rare haplotype, is, however, fixed in Belgians, and Clydesdales. This locus has been associated with divergent fetal growth in cattle.



Other variants enriched in the Idiopathic Abortion cohort:

Locus	Animals with Allele			Allele Frequency in 534 horses*
chr2:65482703	3 E17802-1	E178323-2	E19512-2	0.117
chr4:19365862	3 E17802-1	E17826-1	E178323-2	0.023
chr11:58891156	3 E17607-1	E17826-1	E178323-2	0.068
chr21:15693378	3 E16349DNA2	E17802-1	E19427-1	0.035
chr21:15782369	3 E16349DNA2	E17802-1	E19427-1	0.034
chr21:15828029	3 E16349DNA2	E17802-1	E19427-1	0.036
chr21:16262923	3 E16349DNA2	E17802-1	E19427-1	0.029
chr21:16262935	3 E16349DNA2	E17802-1	E19427-1	0.029
chrX:108317357	3 E17532-1	E17826-1	E178323-2	0.063

BAM and Filtered VCF files

* Durward-Akhurst SA, Schaefer RJ, Grantham B, Carey WK, Mickelson JR, McCue ME. Genetic Variation and the Distribution of Variant Types in the Horse. Front Genet. 2021 Dec 2;12:758366. doi: 10.3389/fgene.2021.758366. PMID: 34925451; PMCID: PMC8676274.

Acknowledgements

AG2PI Seed Grant: A genetic data portal to enable discovery of deleterious genetic variants in farmed animals." Source: Iowa State University, Parent grant USDA/NIFA (20217041235233)

2022-2023 Undergraduate Research Award (UK Office of Undergraduate Research) Arias PI