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Genome-wide Association Studies and Genomic Prediction for Resilience Traits to Aleutian Disease in Mink

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Abstract

Aleutian disease (AD) is a significant health concern for mink, resulting in substantial economic losses for the mink industry. Although phenotypic selection of AD-resilient mink is practiced by some mink farms, the genetic architecture of AD resilience and the potentials of genetic or genomic selection for AD resilient traits have not been widely explored. Thus, the objectives of this study were to conduct genome-wide association studies (GWAS) to identify genomic regions and genes associated with AD resilience and investigate the efficiency of different genetic/genomic methods in predicting breeding values. The studied individuals (n=1,411) had genotypes from the Axiom Affymetrix Mink 70K single nucleotide polymorphism (SNP) panel, with phenotypes including two immune response traits measured by antigen-based enzyme-linked immunosorbent assay (ELISA-G) and iodine agglutination test (IAT) and two feed-intake-related resilience traits measured by the daily variation in feed intake (Varf) and proportion of off-feed days (DOF). The methods of genetic and genomic predictions were traditional pedigree-based best linear unbiased prediction (BLUP), genomic BLUP (GBLUP), and single-step genomic BLUP (ssGBLUP). From the GWAS, seventeen, eight, and seven significant ($q < 0.01$) SNPs were associated with ELISA-G, IAT, and DOF, respectively, and 141, 44, and 42 genes were annotated using these significant. These GWAS analyses help provide a better understanding of the genetic architecture underlying AD resilience in mink and the potential for improving AD resilience using marker-assisted selection. In genetic and genomic prediction analyses, ssGBLUP had the highest prediction accuracy among all methods for IAT (0.53) and Varf (0.32). BLUP outperformed all genomic methods and produced the highest prediction accuracies for ELISA-G (0.71) and DOF (0.22). In the future, the availability of larger training populations, together with declining genotyping and sequencing costs and improved comprehension of genome and variant functional annotations, ssGBLUP is expected to emerge as the most effective approach for genomic prediction of AD resilience in mink.

Keywords: Aleutian disease, American mink, Genome-wide association studies, Genomic predictions, Immune response, Resilience

Introduction

Aleutian disease (AD), caused by the Aleutian mink disease virus (AMDV), is one of the most severe health issues for mink farming and brings huge financial losses to the mink industry [1-5]. Several methods, including vaccination, treatment, and culling strategies, have been attempted to control AD but ended with failure. Thus, mink farmers attempt to control AD by phenotypically selecting AD-resilient mink based on AD tests and/or AD-resilient indicator traits, such as feed intake, pelt quality, and reproductive performance [1,6-9].

Disease resilience is an ability of an animal to mitigate the effects of challenges such as disease or environmental stress (e.g. heat or nutritional) and to maintain its performance [10,11]. A reliable and practical disease resilience indicator trait genetically correlated with health traits is essential for the genetic selection of healthy animals. AD has been determined to be an immune complex disease, where specific antibodies produced against AMDV fail to neutralize the virus and instead form complexes with the infectious virus, resulting in damage to the mink's glomerular and arterial systems [12-15]. Thus, the higher the levels of anti-AMDV antibodies produced, the more severe the infection caused by AMDV [16-20]. Immune response is an important biological component of disease resilience because it affects the capacity of the host to control infection and reduce its adverse consequences. AD represents a special case because it is a persistent viral disease for which effective vaccination, treatment, and eradication strategies are limited. Therefore, evaluating both immune response and overall resilience is particularly relevant to the genetic improvement of mink exposed to AMDV. Thus, immune response measuring by anti-AMDV antibody level was suggested as AD-resilience indicator traits [21,22]. Several mink farms in the Canadian province of Nova Scotia select AD-resilient mink based on productive performance and the iodine agglutination test (IAT), which measures the level of gamma globulin [9]. More recently, some AD-positive mink farms in North America and Europe utilized enzyme-linked immunosorbent assay tests (ELISA), which quantify the antibody levels against AMDV, to select AD-resilient mink [6-8]. Meanwhile, AMDV infection was also found to cause adverse influences on body weight growth [3], feed intake [23,24], pelt quality [1], and female reproductive performance [2,4]. Thus, growth, feed intake, and female reproductive performance were also suggested as AD-resilience indicator traits [21,22]. Although the phenotypic selection of AD-resilient mink is conducted by some mink farms, the genetic architecture of AD resilience has not been widely explored. The estimated heritabilities of the AD-resilience traits were low to moderate, including 0.31 for ELISA-G, 0.18 for IAT, 0.08 for CIEP, 0.09 for DOF, and 0.16 for Varf, indicating the presence of additive genetic variation and the potential for improving these traits through genetic selection [21,22].

Genome-wide association studies (GWAS) and genomic prediction (GP) are powerful tools in animal breeding: GWAS is used to understand the genetic architecture controlling complex traits, whereas GP uses genome-wide marker information to predict genomic estimated breeding values for genetic evaluation and selection. Immune response and disease resilience traits are usually quantitative traits with complex genetic architectures [25-29]. In recent years, with the development of next-generation sequencing technologies, high-density single nucleotide polymorphism (SNP) arrays, and bioinformatic tools, GWAS have become increasingly popular for detecting genetic variants and genes associated with immune response and disease resilience traits in livestock. For example, in swine, several SNPs and genes were found to be related to the resilience to porcine reproductive and respiratory syndrome [30-32], *Mycoplasma hyopneumoniae*

[33], and polymicrobial disease [34] using GWAS. In cattle, several studies conducted GWAS and found several SNPs and genes associated with resilience to paratuberculosis [35]. In poultry, Psifidi et al. [36] conducted GWAS to find the SNPs and genes associated with the immune response to four infectious diseases (infectious bursal disease, Marek's disease, fowl typhoid, and fowl cholera) and resistance to *Eimeria* and cestode parasitism. However, no GWAS on mink immune response to AD and AD-resilience indicator traits has been conducted using genotype data. As for GP, it aims to estimate the breeding values using the genomic diversity captured by extensive markers distributed across the genome without knowing the locations of specific genes [37]. GP accelerates genetic progress by increasing the accuracy of selection and reducing generation intervals. The increase in selection accuracy is particularly important for traits with low heritabilities where the progress made by traditional pedigree-based selection is slow [38]. The heritabilities of disease-related traits are usually low-to-moderate. Therefore, genomic selection is suggested to improve disease-related traits [39,40]. For example, genomic selection studies have been conducted for swine resistance to porcine reproductive and respiratory syndrome [41,42], and moderate genomic prediction accuracies were observed. The common methods used to conduct genomic prediction studies are genomic best linear unbiased prediction (GBLUP) and single-step GBLUP (ssGBLUP) approaches. GBLUP is a multi-step method using genomic information to predict genomic breeding values [43,44]. For this purpose, a genomic relationship matrix, which is created using DNA marker information instead of pedigree, is applied and expected to provide more accurate predictions of genetic merit than the traditional pedigree-based best linear unbiased prediction (BLUP) method [45]. Compared with GBLUP, ssGBLUP is a single-step methodology that combines pedigree, phenotypic and genomic information of all breeding individuals for genetic evaluation in one model [46]. Meanwhile, ssGBLUP was generally found to be simpler, faster, and more accurate than multistep methods [46-48]. Genomic selection has the potential to improve the AD resilience in mink since the AD resilience traits are difficult and expensive to measure and have low-to-moderate heritability [21,22]. However, no genomic prediction studies have been conducted for AD resilience in mink.

The chromosome-level genome assembly by Karimi et al. [49] and the development of the first Axiom Affymetrix Mink 70K SNP panel for American mink [50] have made the GWAS and GP in AD resilience in mink feasible. Thus, this study aimed to 1) conduct GWAS to identify genomic regions associated with AD resilience traits in mink; and to 2) evaluate the accuracy of three methods, including traditional pedigree-based BLUP, GBLUP, and ssGBLUP, in prediction AD resilience traits in mink to determine the best method for each trait. To our knowledge, this is the first study to integrate genotype-based GWAS with genetic and genomic prediction for both immune-response and feed-intake-related resilience traits associated with AD in mink, providing new information on their genomic architecture and potential for genetic selection.

Results

Summary Information of Phenotype Data and Genotype Data

Following the data-processing and quality-control procedures described in the Methods section, the descriptive statistics and final numbers of animals and SNPs retained for analysis are summarized below.

Descriptive statistics of the de-regressed estimated breeding values (dEBV), which were computed from the estimated breeding values (EBVs) obtained from the study by Hu et al. [21], for four

traits analyzed by GWAS are presented in Table 1. A total of 1,120, 1,114, 890, and 890 animals were used in the final GWAS for antigen-based ELISA (ELISA-G), IAT, proportion of off-feed days (DOF), and daily variation in feed intake (Varf), respectively. The coefficient of variation (CV) of studied traits ranged from 4.4 to 93.5%, where IAT had the lowest CV, and Varf had the highest CV (Table 1).

Table 1. The descriptive statistics of dEBVs for four traits analyzed by GWAS.

Traits ¹	Total animals	Mean	SD	Range	CV
ELISA-G	1,120	-0.167	2.296	-4.951 to 6.814	13.749
IAT	1,114	0.122	0.532	-1.496 to 1.991	4.361
DOF	890	0.002	0.018	-0.054 to 0.064	9.000
Varf	890	-0.067	6.264	-20.26 to 19.797	93.493

¹ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; DOF = Proportion of off-feed days; Varf = Variation in daily feed intake; SD = Standard deviation; CV= Coefficient of variation.

The number of records, mean, standard deviation (SD), range, and coefficient of variation (CV) for each trait used in genetic and genomic predictions are presented in Table 2. Among all studied traits, ELISA-G (n=1,421) and IAT (n=1,409) had the most phenotypes recorded because the Canadian Centre for Fur Animal Research (CCFAR) started recording these two traits in 2013, while DOF (n=890) and Varf (n=890) were recorded after 2018. The CVs of ELISA-G (157%), IAT (148%), and DOF (153%) were all higher than 100%, while Varf (25%) had CVs less than 50%.

Table 2. The descriptive statistics of four studied traits used in genetic and genomic predictions.

Traits ¹	Phenotype records	Mean	SD	Range	CV (%)
ELISA-G	1,421	1.40	2.20	0 to 7	157%
IAT	1,409	0.68	1.01	0 to 4	148%
DOF	890	5.42	8.30	0 to 65.45	153%
Varf	890	48.31	12.06	27.37 to 136.68	25%

¹ELISA-G=Aleutian mink disease virus antigen-based enzyme-linked immunosorbent assay test; CIEP=Counterimmunoelectrophoresis test; IAT=Iodine agglutination test; DOF=the proportion of off-feed days; Varf=Variation in daily feed intake; SD=Standard deviation; CV=Coefficient of variation.

Among the 62,375 SNPs, 3,180 SNPs are located on sex chromosomes and thus were removed from the analysis because the present GWAS and genomic prediction models were designed for autosomal markers. Sex chromosomes have sex-specific inheritance patterns and ploidy and would require additional genotype coding and modeling procedures. A total of 4,396 SNPs were removed due to genotype rate < 0.1; 26,387 SNPs due to minor allele frequency < 0.05; and 2,223 SNPs due to Hardy-Weinberg equilibrium with very low probability (1×10^{-6}). No individual was excluded due to a low (<90%) call rate. Finally, 26,189 SNPs and 1,356 animals remained and were used for further analyses. The density distributions of the filtered SNPs across the genome are shown in Figure 1. The relatively low SNP density in the first half of chromosome 8 reflects the limited marker coverage of this genomic region in the original Axiom Affymetrix Mink 70K

SNP panel, which was the first SNP array developed for American mink, rather than an absence of genetic variation in this region.

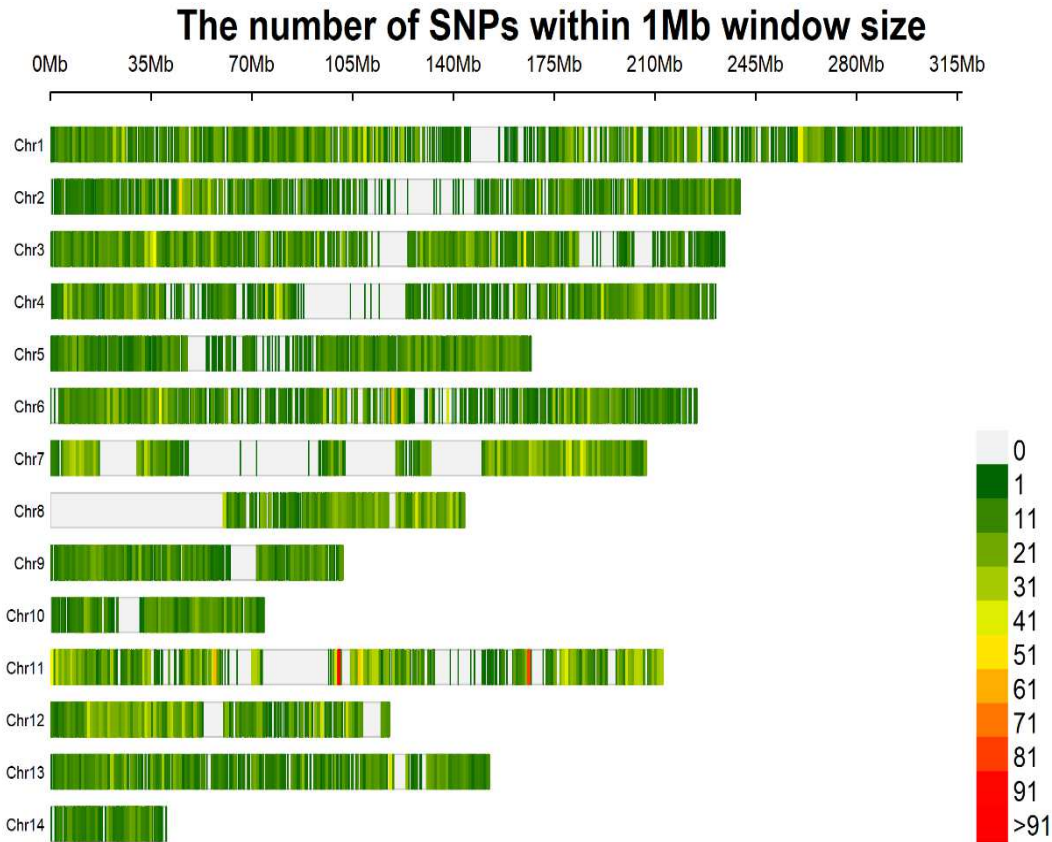


Figure 1. The filtered SNP density distributions on *Neogale vison* chromosomes. The horizontal axis (x-axis) shows the chromosome length (Mb). Color index indicates the number of labels.

Genome-wide Association Studies

The Q-Q plots of all studied traits were drawn, and the genomic inflation factors of all studied traits were calculated since population stratification could have an impact on GWAS. The Q-Q plot of each trait was shown following the Manhattan plot of the corresponding trait (Figure 2). For all studied traits, the observed $-\log(p\text{-values})$ were fairly close to the expected $-\log(p\text{-values})$ (Figure 2). In the meantime, the genomic inflation factors for all studied traits were close to 1 (ranging from 0.95 to 0.98). The Q-Q plots and genomic inflation factors results indicated that the influence of population stratification was negligible, and there were little or no residual population structure effects on the test statistic inflation in this study.

The significant ($q < 0.01$) SNPs for each studied trait are illustrated in Figure 2, and their chromosomes, physical positions, $-\log(p\text{-values})$, frequencies, substitution effects, and percentage of dEBV variance explained are provided in Table 3. For ELISA-G, 17 SNPs, which were distributed on chromosomes 1, 4, 6, and 13, were detected to be significant (threshold $p\text{-value} =$

1.76 $\times 10^{-4}$) with substitution effects ranging from -1.823 to 1.723 (Figure 3 and Table 3). These significant SNPs individually explained 0.048% to 0.094% of the dEBV variance of ELISA-G, and together they explained 1.252% of the dEBV variance of ELISA-G (Table 3). Eight genome-wide SNPs with substitution effects ranging from -0.313 to 0.366 were detected to be significant (threshold p-value = 1.13×10^{-4}) for IAT, and these eight SNPs were distributed on chromosomes 2, 3, and 6 (Figure 3 and Table 3). These eight significant SNPs explained 0.799% of the dEBV variance of IAT, and a single SNP could explain 0.084 to 0.115% of the dEBV variance of IAT (Table 3). For DOF, seven SNPs, which were distributed on chromosomes 1, 4, 5, 11, and 14, were detected to be significant (threshold p-value = 9.13×10^{-4}). These significant SNPs had substitution effects ranging from 0.006 to 0.100 and could explain 0.029 to 0.084% of the dEBV variance of DOF individually. Together, these significant SNPs accounted for a total of 0.405% of the dEBV variance of DOF.

No significant ($q > 0.01$, threshold p-value = 1.07×10^{-4}) SNP was detected for Varf (Figure 2). This may partly reflect the relatively low heritability of Varf (0.16) and the limited sample size available for GWAS ($n = 890$), which reduce statistical power to detect variants with small effects. In addition, Varf is derived from within-individual fluctuations in daily feed intake and therefore may capture substantial environmental and short-term variation in addition to genetic variation. Although measurement error could also contribute to this variability, its effect was not separately quantified in the present study. These factors, together with the potentially polygenic architecture of Varf, may have limited the detection of significant SNP associations.

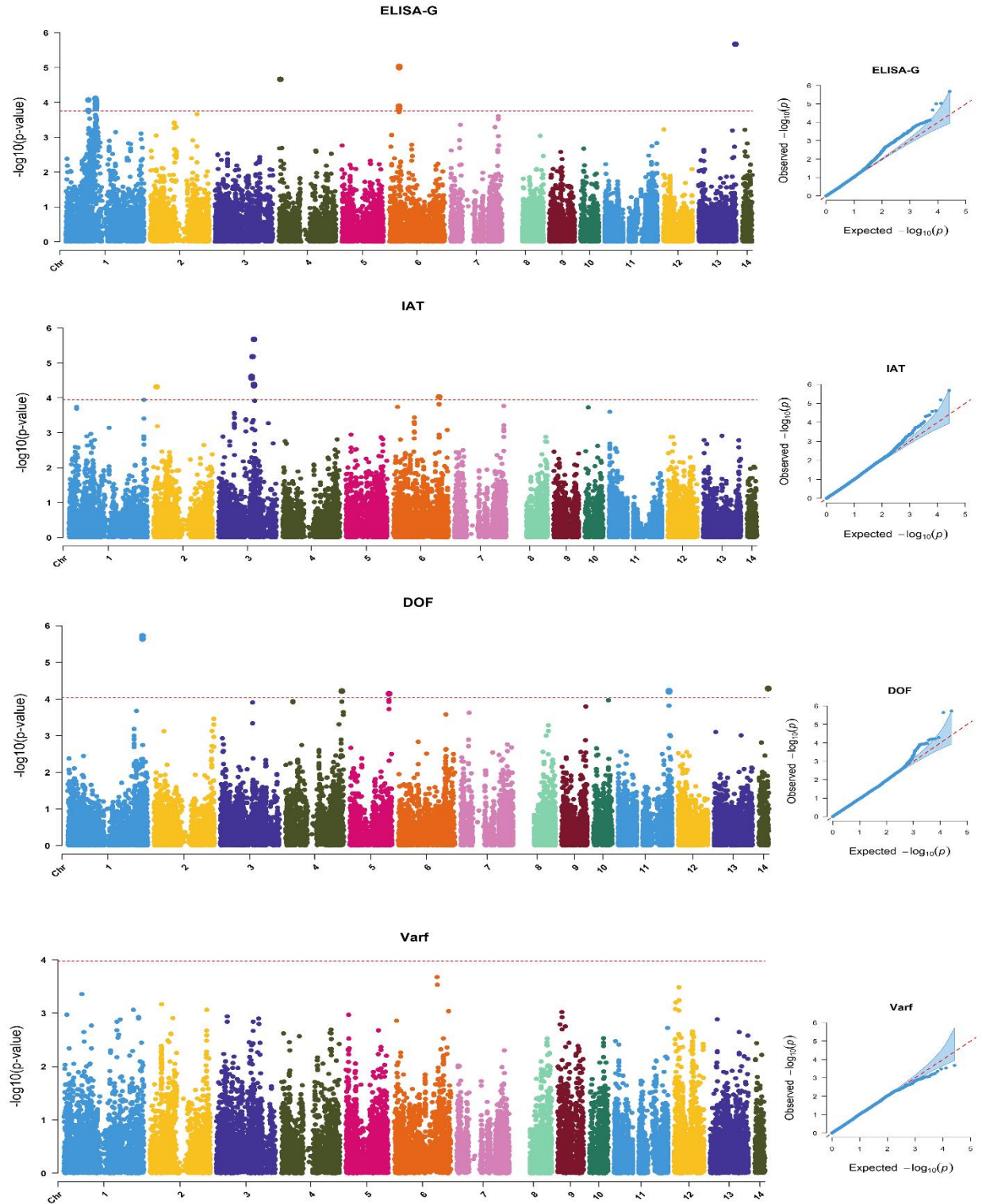


Figure 2. Manhattan plots and Quantile-Quantile plots for four studied traits. The X-axis is the position of SNP on each chromosome, and the Y-axis is the significant level ($-\log_{10} p$ value). The red lines indicate significant thresholds. There were 17, 8, 7 and 0 SNPs that passed the significant thresholds for enzyme-linked immunosorbent assay test (ELISA-G), Iodine agglutination test (IAT), proportion of off-feed days (DOF), and variation in daily feed intake (Varf) trait, respectively.

Table 3. Summary information of significant ($q < 0.01$) SNPs for enzyme-linked immunosorbent assay test, iodine agglutination test, and off-feed days traits.

Traits ¹	Chr ²	Physical position (bp)	$-\log_{10}$ (p-value)	Allele frequency	Allele substitution effect	% dEBV ³
ELISA-G	1	91,348,258	3.772	0.695	1.309	0.048
	1	91,563,695	4.068	0.708	1.400	0.055
	1	119,668,108	4.112	0.683	1.552	0.068
	1	121,737,422	3.817	0.692	1.685	0.080
	1	121,755,885	3.961	0.691	1.711	0.083
	1	121,873,249	4.045	0.683	1.658	0.078
	1	121,899,199	3.916	0.692	1.702	0.082
	1	121,970,625	3.862	0.691	1.693	0.081
	1	121,976,198	3.862	0.691	1.693	0.081
	1	122,009,542	3.983	0.693	1.723	0.084
	1	122,459,883	3.928	0.692	1.710	0.083
	4	5,758,929	4.664	0.917	-1.685	0.080
	6	39,873,751	3.895	0.914	-1.584	0.071
	6	39,952,440	3.823	0.887	-1.348	0.051
	6	39,973,150	5.030	0.912	-1.819	0.094
	6	39,976,387	5.000	0.913	-1.823	0.094
	13	149,480,595	5.670	0.733	-1.166	0.038
IAT	2	13,247,909	4.316	0.935	0.359	0.111
	3	133,845,792	4.612	0.924	0.366	0.115
	3	133,851,626	4.563	0.924	0.363	0.113
	3	137,464,576	5.179	0.906	0.339	0.099
	3	142,608,584	4.386	0.906	0.318	0.087
	3	142,738,773	5.677	0.898	0.352	0.106
	3	142,775,506	4.348	0.906	0.316	0.086
	6	185,881,210	4.026	0.914	-0.313	0.084
DOF	1	296,396,353	5.640	0.876	0.010	0.082
	1	296,406,380	5.722	0.878	0.010	0.084
	4	223,648,486	4.213	0.908	0.009	0.067
	5	155,691,399	4.141	0.517	0.006	0.029
	11	201,098,313	4.194	0.853	0.008	0.048
	11	201,105,005	4.223	0.835	0.007	0.044
	14	38,377,828	4.284	0.893	0.008	0.052

¹ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; DOF = Proportion of off-feed days.

² Chromosome.

³ The percentage of dEBV variance explained by the SNP.

Gene Annotation and Gene Ontology of Significant SNPs

The candidate genes annotated from the significant SNPs for ELISA-G, IAT, and DOF are listed in Supplementary S1. A total of 141, 44, and 42 unique candidate genes were annotated from the significant SNPs for ELISA-G, IAT, and DOF, respectively (Supplementary Table S1). The annotated genes, which have available information in the existing literature, are listed in Supplementary Table S2. For ELISA-G, 67, three, and five unique genes were detected on chromosomes 1, 6, and 13, respectively. For IAT, 20 and seven unique genes were annotated on chromosomes 1 and 3, respectively. Regarding DOF, the annotated genes were distributed on chromosomes 1, 3, 7, 10, and 11, where one, five, six, seven, and two unique genes were detected, respectively.

The functional classifications of candidate genes are shown in Figure 3. The cellular anatomical entity and protein-containing complex were the two GO:CCs detected for all three traits, and the cellular anatomical entity was the major one (occupied more than 72% of the detected cellular components) in all the cases (Figure 3). For ELISA-G, the annotated genes were classified into 13 GO:BPs and eight GO:MFs. Among the 13 GO:BPs, cellular process, metabolic process, and biological regulation were the top three BPs, and growth, immune system process, and reproduction, which are related to AD resilience indicator traits, were also included but with smaller proportions. The genes annotated from IAT were classified into 11 GO:BPs, and again cellular process, metabolic process, and biological regulation were the top three BPs, and seven GO:MFs of binding, catalytic activity, and transporter activity were the top three MFs. The growth, immune system process, and reproduction were also included in the detected GO:BPs, but they occupied smaller proportions. Regarding DOF, the annotated genes were classified into eight GO:BPs, and cellular process, metabolic process, and biological regulation were also the top three BPs, and five GO:MFs, with binding, catalytic activity, and transporter activity were the top three MFs.

The overrepresentation tests of annotated genes were conducted for ELISA-G, IAT, and DOF, but significant ($q < 0.05$) overrepresentations were only detected in ELISA-G. The overrepresentations of candidate genes related to ELISA-G are presented in Table 4. In total, five significant ($q\text{-value} < 0.05$) overrepresented GO enrichment terms, including four GO:CCs (TAP complex, Classical-complement-pathway C3/C5 convertase complex, MHC class I peptide loading complex, and Extracellular region) and one GO:MF (ABC-type peptide transporter activity), were detected for ELISA-G (Table 4). No significant ($q < 0.05$) KEGG pathways of candidate genes were detected for all studied traits.

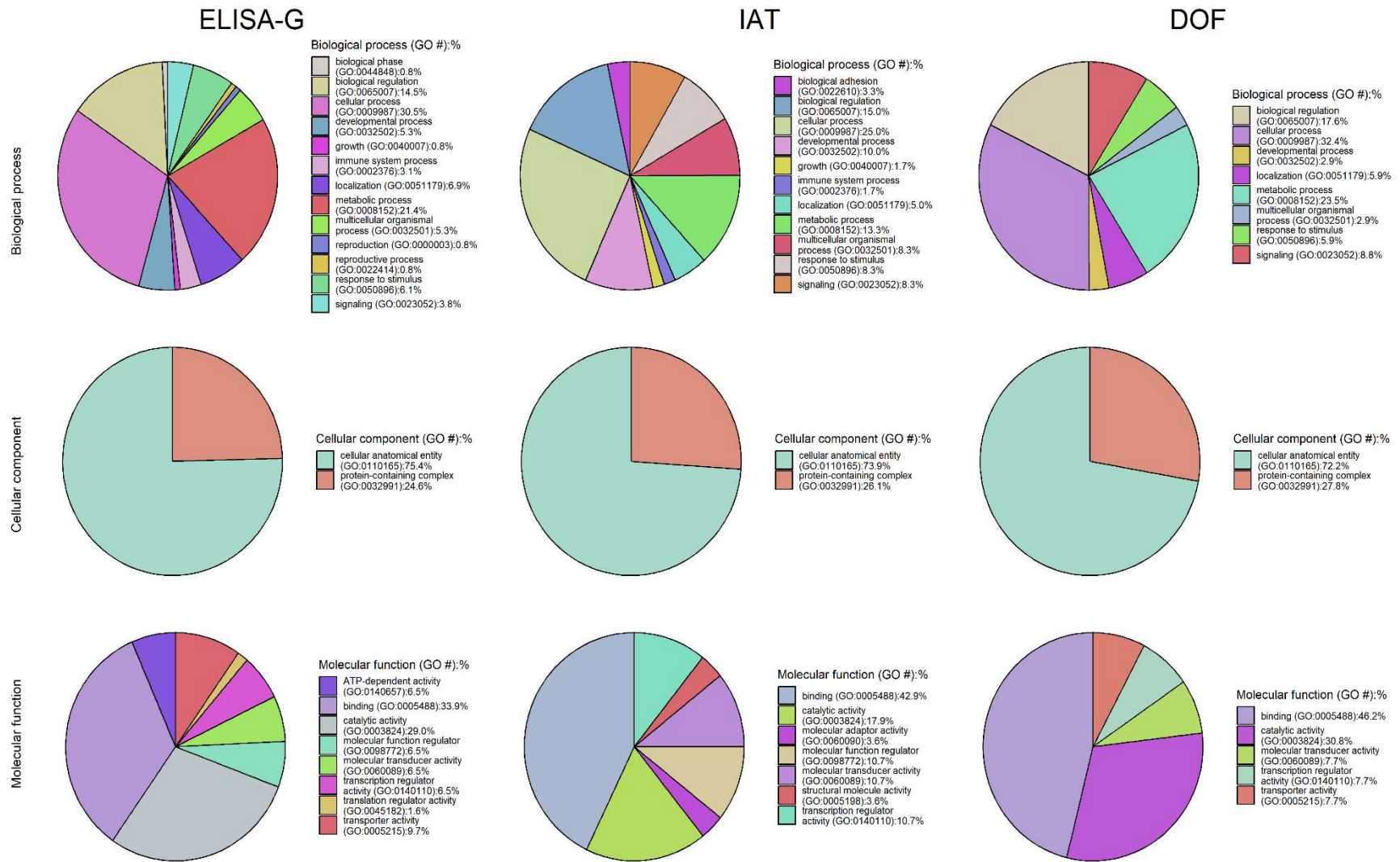


Figure 3. The pie charts of functional classifications (molecular function, cellular component, and biology process) of candidate genes related to significant ($q < 0.05$) SNPs for AMDV-G based enzyme-linked immunosorbent assay test (ELISA-G), iodine agglutination test (IAT), and the proportion of off-feed days (IAT).

Table 4. Significant (false discovery rate adjusted p-value<0.05) functional enrichment of candidate genes detected from enzyme-linked immunosorbent assay test trait.

Gene ontology term	GO ID	Annotation set	q-value
TAP complex	0042825	Cellular component	0.002
Classical-complement-pathway C3/C5 convertase complex	0005601	Cellular component	0.002
MHC class I peptide loading complex	0042824	Cellular component	0.006
Extracellular region	0005576	Cellular component	0.007
ABC-type peptide transporter activity	0015440	Molecular function	0.014

Estimation of Genetic Parameters

The variance components (SE) and heritabilities of studied traits, which were estimated by using traditional BLUP model (**Model 1**) and full dataset (all available phenotypes), are represented in Table 5. The heritabilities of the five studied traits were low to moderate, where ELISA-G had the highest heritability (0.31) and CIEP showed the lowest heritability (0.08). The heritabilities of IAT, DOF, and Varf were 0.18, 0.09, and 0.16, respectively.

Table 5. Estimates of variance components and heritabilities with their standard errors (SE) for all studied traits using traditional best linear unbiased prediction model and full dataset.

Traits ¹	Variance components				Heritabilities
	$\sigma_a^2 \pm \text{SE}$	$\sigma_m^2 \pm \text{SE}$	$\sigma_{pe}^2 \pm \text{SE}$	$\sigma_e^2 \pm \text{SE}$	h^2
ELISA-G	1.49±0.43	0.87±0.25	1.16±0.26	1.31±0.11	0.31
IAT	0.18±0.05	NA ²	0.18±0.06	0.63±0.05	0.18
DOF	5.79±3.58	NA	NA	60.59±4.11	0.09
VarF	19.58±9.89	NA	NA	104.50±9.54	0.16

¹ELISA-G = antigen-based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; CIEP = Counterimmunoelectrophoresis test; DOF = the proportion of off-feed days; VarF = Variation in daily feed intake. σ_a^2 = additive genetic variance; σ_m^2 = maternal genetic variance; σ_{pe}^2 = permanent environmental variance; σ_e^2 = residual variance.; h^2 = heritability.

²NA = not applicable.

The estimations of variance components (SE) and heritabilities for all studied traits from three different prediction models (BLUP, GBLUP, and ssGBLUP) using the validation dataset are shown in Table 6. For ELISA-G, the BLUP model showed the highest estimated heritability (0.31), while the GBLUP model showed the lowest estimated heritability (0.17), which was lower than the heritability estimated by the ssGBLUP model (0.20). For IAT, both BLUP and ssGBLUP models showed a heritability of 0.16, which was slightly lower than the heritability estimated by the GBLUP model (0.15). For DOF, the estimated heritabilities were 0.09 for the BLUP and GBLUP models, while the ssGBLUP model showed a slightly lower estimation of 0.08. For Varf, the BLUP model estimated a heritability of 0.11, which was slightly lower than the value estimated by GBLUP (0.12) but higher than the value estimated by ssGBLUP (0.08).

Prediction Abilities, Accuracies, and Bias

The prediction abilities and accuracies (SE) of three different prediction models (BLUP, GBLUP, and ssGBLUP) for all studied traits are presented in Table 7. For ELISA-G, the BLUP model showed the highest prediction ability (0.39) and accuracy (0.71), while GBLUP and ssGBLUP models showed slightly lower prediction abilities (0.37 and 0.38, respectively) and accuracies (0.66 and 0.68, respectively). For IAT, ssGBLUP showed the highest prediction ability (0.22) and accuracy (0.53), while GBLUP model showed the lowest prediction ability (0.15) and accuracy (0.34), which was also lower than the prediction ability (0.18) and accuracy (0.41) of BLUP model. For DOF, the ssGBLUP model showed a prediction ability of 0.05 and an accuracy of 0.17, which were lower than the BLUP model (0.07 and 0.22, respectively) but higher than the GBLUP model (0.03 and 0.11, respectively). For Varf, the ssGBLUP models showed a highest prediction ability of 0.11 and accuracy of 0.32, which were similar to the GBLUP model (0.10 and 0.30, respectively) but higher than the BLUP model (0.08 and 0.23, respectively).

The prediction biases of all prediction models for each trait, which were measured by the regression of adjusted phenotypes on the predicted breeding values, are shown in Table 8. For ELISA-G, the ssGBLUP model showed the smallest prediction bias (1.34), while the BLUP model showed the largest prediction bias (1.55), which was higher than the prediction bias of the GBLUP model (1.35). For IAT, the BLUP model showed the smallest prediction bias (1.09), while the GBLUP model showed the largest (1.67). The ssGBLUP model was the only model with a prediction bias of less than one (0.84) among all prediction models for IAT. For DOF, the BLUP and GBLUP models had a prediction bias larger than the ssGBLUP model (0.80 and 0.65, respectively), where the ssGBLUP model showed the smallest prediction bias (1.05). For Varf, the GBLUP model had a prediction bias of 1.33, which was smaller than the prediction bias of the ssGBLUP model (1.66) but larger than the prediction bias of the BLUP model (1.07).

Table 6. Estimates of variance components and heritabilities with their standard errors (SE) for all studied traits from three different prediction models using validation dataset.

Trait ¹	BLUP ¹					GBLUP ²			ssGBLUP ³				
	$\sigma_a^2 \pm \text{SE}$	$\sigma_m^2 \pm \text{SE}$	$\sigma_{pe}^2 \pm \text{SE}$	$\sigma_e^2 \pm \text{SE}$	h^2	$\sigma_a^2 \pm \text{SE}$	$\sigma_e^2 \pm \text{SE}$	h^2	$\sigma_a^2 \pm \text{SE}$	$\sigma_m^2 \pm \text{SE}$	$\sigma_{pe}^2 \pm \text{SE}$	$\sigma_e^2 \pm \text{SE}$	h^2
ELISA-G	1.50±0.48	0.80±0.27	1.21±0.30	1.30±0.12	0.31	0.91±0.10	4.41±0.36	0.17	0.97±0.28	1.09±0.27	1.47±0.22	1.29±0.12	0.20
IAT	0.16±0.06	NA	0.19±0.07	0.63±0.06	0.16	0.04±0.04	0.22±0.07	0.15	0.16±0.05	NA	0.18±0.06	0.63±0.06	0.16
DOF	6.26±4.21	NA	NA	59.95±4.75	0.09	5.03±1.31	50.53±3.07	0.09	4.51±3.12	NA	NA	55.52±4.16	0.08
Varf	12.87±8.04	NA	NA	106.82±8.7 2	0.11	10.59±6.7 7	90.65±15.2 7	0.12	9.98±3.88	NA	NA	101.04±7.6 4	0.08

¹BLUP = traditional best linear unbiased prediction; ²GBLUP = multi-steps genomic best linear unbiased prediction; ³ssGBLUP = single-step genomic best linear unbiased prediction.

⁴ELISA-G = antigen-based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; CIEP = Counterimmunoelectrophoresis test; DOF = the proportion of off-feed days; VarF = Variation in daily feed intake.

σ_a^2 = additive genetic variance; σ_m^2 = maternal genetic variance; σ_{pe}^2 = permanent environmental variance; σ_e^2 = residual variance.; h^2 = heritability.

⁵NA = not applicable.

Table 7. The prediction abilities and accuracies and their SE for all studied traits from three different prediction models using validation dataset.

Trait ⁴	BLUP ¹		GBLUP ²		ssGBLUP ³	
	Prediction ability	Prediction accuracy	Prediction ability	Prediction accuracy	Prediction ability	Prediction accuracy
ELISA-G	0.39 (0.03)	0.71 (0.05)	0.37 (0.02)	0.66 (0.04)	0.38 (0.02)	0.68 (0.04)
IAT	0.18 (0.02)	0.41 (0.05)	0.15 (0.04)	0.34 (0.09)	0.22 (0.05)	0.53 (0.11)
DOF	0.07 (0.03)	0.22 (0.11)	0.03 (0.01)	0.11 (0.03)	0.05 (0.02)	0.17 (0.09)
Varf	0.08 (0.02)	0.23 (0.06)	0.10 (0.02)	0.30 (0.04)	0.11 (0.06)	0.32 (0.05)

¹BLUP = traditional best linear unbiased prediction; ²GBLUP = multi-steps genomic best linear unbiased prediction; ³ssGBLUP = single-step genomic best linear unbiased prediction.

⁴ELISA-G = antigen-based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; CIEP = Counterimmunoelectrophoresis test; DOF = the proportion of off-feed days; VarF = Variation in daily feed intake.

Table 8. Regression coefficient and their standard errors of adjusted phenotypes on the predicted breeding value (EBV or GEBV) from three different prediction models using validation dataset for all studied traits.

Trait ¹	BLUP ²	GBLUP ³	ssGBLUP ⁴
ELISA-G	1.55 (0.22)	1.35 (0.21)	1.34 (0.22)
IAT	1.09 (0.54)	1.67 (0.60)	0.84 (0.27)
DOF	0.80 (0.53)	0.65 (0.30)	1.05 (0.75)
Varf	1.07 (0.76)	1.33 (0.61)	1.66 (0.65)

¹ELISA-G = antigen-based enzyme-linked immunosorbent assay test; IAT = Iodine agglutination test; CIEP = Counterimmunoelectrophoresis test; DOF = the proportion of off-feed days; VarF = Variation in daily feed intake.

²BLUP = traditional best linear unbiased prediction; ³GBLUP = multi-steps genomic best linear unbiased prediction; ⁴ssGBLUP = single-step genomic best linear unbiased prediction.

Discussion

Candidate Genes for ELISA-G

A total of 141 genes were found to be related with immune response measured by ELISA-G. Among them, three genes, including *MPIG6B*, *RUNX2*, and *C4A*, were found to be related to the immune system process and might have important roles in immune-mediated responses to AMDV infection (Figure 3 and Supplementary Table S2). The *MPIG6B*, also known as *G6B* or *C6orf25*, is localized in the class III region of the MHC, which is a region known to contain many genes associated with the immune system [51,52]. *MPIG6B* plays a critical role in regulating megakaryocytic function and platelet production [52,53], and loss-of-function of *MPIG6B* can cause severe thrombocytopenia, myelofibrosis, and anemia in both humans and mice [51,54-58]. The detection of *MPIG6B* in this study may be related to the severe platelet decrease [59] and anemia [60] caused by AD. The *RUNX2* gene is well-known as an important regulator of bone

development, where it acts as an activator in the generation of osteoblasts and chondrocyte differentiation [61], but it also plays an important role in the immune system process. The *RUNX2* gene was found to regulate the development and homeostasis of plasmacytoid dendritic cells [62,63], which play a crucial role in antiviral immunity and may implicate initiating and developing immune-mediated diseases [64,65]. In the meantime, *RUNX2* was found to play an important role in early T cell development [66] and the long-term maintenance of antiviral memory CD8+ T cells [67]. The identification of *RUNX2* may be related to the immune-mediated nature of AD and the proliferation of CD8+ T cells after AD infection [68]. *C4A* is one of the two genes (*C4A* and *C4B*) that encode for the complement component C4, which is a key protein involved in the classical pathway of the complement system [69]. The complement system is involved in several immune functions, including the recognition and elimination of pathogens, the clearance of damaged cells, and the modulation of inflammatory responses [70]. *C4A* shows preferential binding to the targets containing free amino groups, such as immune complex [71], with a role in the clearance of the immune complex [72]. Deficiency of *C4A* has been found to cause less effective immune complex processing, resulting in the deposition of these complexes in tissues and subsequent damage [73]. AD has been defined as an immune complex disease [12]; thus, the detection of the *C4A* gene in this study may relate to the characteristics of AD. These three genes were also detected by the selection signatures study related to immune response of mink to AD [74], which indicated these genes may play critical roles in the immune response of mink to AD.

Candidate Genes for IAT

A total of 44 genes were annotated from the significant ($q < 0.01$) SNPs associated with IAT in this study. Among them, two genes, *TNFRSF11A* and *C4A*, were related to the immune system process (Figure 3 and Supplementary Table S2). The *TNFRSF11A* gene, which is also known as *the nuclear factor- κ B receptor activator* [75], was identified in both immune system and skeletal system [76,77]. This gene was found to be related to the production of immunoglobulin in humans [78]. Hypergammaglobulinemia is one of the typical symptoms of AD [79,80], and thus may explain the detection of *TNFRSF11A* in this study. The *TNFRSF11A* gene has been determined as the cause of autosomal recessive osteopetrosis in humans [78,81]; however, whether AD could cause skeletal-related issues is unknown, which is worth further investigation in the future. The *C4A* was found to have a greater affinity for the immunoglobulin molecules in immune complexes [71,82,83]; thus, the hypergammaglobulinemia caused by AD, which is the overproduction of more than one class of immunoglobulins by plasma cells, could be the reason *C4A* gene was detected for IAT.

Candidate Genes for DOF

A total of 42 genes were found to be related to DOF in this study. Among them, two genes, *ADCY7* and *CNDP2*, were found to be associated with feed intake in livestock or appetite in humans. The *ADCY7* gene was found to be associated with appetite in swine in previous studies [84,85]. In the meantime, *ADCY7* was associated with depression in mice and humans [86,87], which indicates the lower appetite of mink in AD-positive farms may be caused by a mood disorder. However, the relationship between AD and depression was not identified yet, which is worth further investigation. The *CNDP2* gene was found to be involved in the production of N-lactoyl-

phenylalanine [88], which has been thought to suppress feeding in mice [89]. Feed intake is influenced by multiple dynamic physiological signals that are regulated by the metabolic and physiological conditions of animals [90-92]. Thus, AD may affect the feed intake frequency or appetite of mink by affecting the metabolism, which needs further studies to explore.

Overrepresentations of Candidate Genes for ELISA-G

A total of five significant ($q\text{-value} < 0.05$) overrepresented GO enrichment terms, including four cellular components (TAP complex, Classical-complement-pathway C3/C5 convertase complex, MHC class I peptide loading complex, and Extracellular region) and one molecular function (ABC-type peptide transporter activity), were detected for ELISA-G (Table 4). Among them, TAP (transporter associated with antigen processing) complex, MHC (major histocompatibility complex) class I peptide loading complex, and ABC-type (ATP-binding cassette) peptide transporter activity are closely correlated and play important roles in the adaptive immune response against virally or malignantly transformed cells. The TAP complex is a superfamily of ABC transporters and plays a crucial role in the processing and presentation of the MHC class I restricted antigens, which present their antigenic peptides to CD8⁺ cytotoxic T-lymphocytes and eventually induce the elimination of virally or malignantly transformed cells [93-96]. The cellular immune response of mink to AMDV infection has not been properly defined so far, and the detection of these GO terms may help further research into the cellular immune response to AD. The C3/C5 convertase is an essential component of the complement system, which is an immune defense mechanism present in the blood plasma to combat pathogens [70,97]. The classical-complement-pathway C3/C5 convertase complex pathway activates the proteases C3 and C5 convertase, thereby cleaving the proteins C3 and C5. The cleaved fragments can attract phagocytes to the site of infection and label target cells for elimination by phagocytosis [70,97]. The presence of immune complexes could activate the complement system, which plays an important role in clearing immune complexes [98-100]. The detection of the classical-complement-pathway C3/C5 convertase complex pathway may be related to the responses of the complement system to the formation of immune complexes caused by AD, as the deposition C3 was detected in AD-infected mink [101,102].

Genetic and Genomic Predictions

The advantage of using genomic information (GBLUP and ssGBLUP methods) for breeding value prediction over using pedigree information (BLUP method) was not consistent across the traits studied here. Compared to traditional BLUP method, using genomic information increased the prediction ability and accuracy for the IAT and Varf but not for the ELISA-G and DOF. Genomic predictions for these traits have not been conducted in the previous studies. Thus, no previous estimates are available for comparison. However, similar results were also reported in swine [103], cattle [104], and sheep [105] for feed efficiency and growth traits and immune response traits in chicken [106], where the use of genomic data for genomic prediction was not beneficial for all traits. The usage of genomic information is generally expected to provide better prediction accuracy because genomic data could consider the Mendelian sampling terms better than pedigree information, therefore producing more accurate genetic relationships among animals [107-109]. However, this is not always the case, as mentioned above. Several factors could affect the genomic prediction ability and accuracy, including the ability of markers to capture the total genetic

variance of the traits [110], the accuracy of the estimates of marker effects [110], the density of makers used [103,111], the heritability of the studied trait [110-112], and the population size [112-114].

The traditional BLUP model showed higher prediction ability and accuracy than GBLUP and ssGBLUP models for ELISA-G, which indicated the advantage of using genomic information for breeding value prediction over using pedigree information was not present for ELISA-G. The missing heritability was considered to be one of the main reasons leading to these results. In the case of ELISA-G, the heritabilities estimated by using genomic information were lower than estimates obtained from pedigree-based BLUP model (Table 6), which indicated the existence of missing heritability. Missing heritability has been considered an issue in both human [115,116] and livestock genetics [103,104,106]. Missing heritability could be caused by several reasons, including the incomplete linkage disequilibrium between causal genomic variants and genotyped SNPs [115,116], the genetic architecture of the studied trait, epistatic effects, and genotype-by-environment interactions [117]. For instance, if the genotyped SNPs are located close to causal variants for the traits or the SNPs themselves are actually the causal variants for the traits, the SNPs could capture a large proportion of the genetic variance and provide high genomic prediction ability and accuracy. In another way, if the genotyped SNPs are not able to capture an adequate proportion of the genetic variation for the trait, the prediction accuracy could be limited. In the case of ELISA-G, the genotyped SNPs in our study could only catch 55 to 65% of the genetic variance based on the pedigree-based estimate of heritability (Table 6). Thus, missing heritability could be one of the main reasons for the lower prediction ability and accuracy in the GBLUP and ssGBLUP models compared to the BLUP model for ELISA-G. In the meantime, the different inputs in the models (dEBVs in GBLUP and raw phenotypes in BLUP and ssGBLUP) could also be the reason for different estimated heritabilities, thereby leading to different accuracies among models.

Besides ELISA-G, the traditional BLUP model also showed higher prediction ability and accuracy than GBLUP and ssGBLUP models for the DOF. Different from the case of ELISA-G, where the missing heritability issue existed, the estimated heritabilities from using genomic information were equal to or very close to the estimates from pedigree-based BLUP model (Table 6). However, the low level of heritability of DOF itself, small training population size, and insufficient SNP marker density could be the reasons leading to these results. The accuracy of genomic prediction could be affected by trait heritability, especially for the traits with low heritability (lower than 0.4) [43]. Many studies showed that the heritability of studied traits could strongly influence the accuracy of genomic selection because locus identification and effect estimation are difficult to predict in the case of low heritability quantitative traits [43,103,110-113]. Generally, it is assumed that the target trait with high heritability has good prediction accuracies and vice versa. For low heritable and complex traits, many previous studies showed that the performance of the traditional pedigree-based BLUP model seems to provide better prediction ability and accuracy compared to the prediction models (GBLUP and ssGBLUP) using genomic information [103,104,106,113]. The accuracy of genomic selection is also affected by the size of the training population because the small training population size could cause the model to estimate the marker effects poorly and hence the prediction accuracy [112]. Vanraden et al. [118] found that the correlation between accuracy and the size of training population was nearly linear. In other words, the smaller that the training population size is, the lower accuracy of genomic selection could be observed [110,112,119]. Marker density is another factor that influences the accuracy of genomic selection.

The complete genome could be covered by a minimum number of markers based on the decay of linkage disequilibrium (LD), where at least one marker is expected in LD with each genomic region. The increase in marker density has the potential to improve the accuracy of genomic prediction, as more causative mutations are expected to be included in the increased genotype data [120,121]. It requires a larger training population, a larger number of phenotypes, and a higher density of markers for traits with low heritability to attain a similar level of accuracy and persistence of accuracy as the traits with high heritability [43,114,122,123]. However, in the cases of DOF, where the heritabilities were lower than 0.1 (Table 5), the size of the training population (less than 750), the number of phenotypes records (less than 1,000), and marker density (around 26K after quality control) may not be sufficient to provide satisfactory prediction accuracy in genomic selection methods.

The ssGBLUP had higher or the same prediction ability and accuracy compared to the GBLUP model in all scenarios (Table 7). The ssGBLUP model has the advantage of simultaneously using the phenotypes of genotyped and non-genotyped animals, pedigrees, and genotypes. Compared with GBLUP model, ssGBLUP model predicts how non-genotyped individuals can benefit from genomic information by applying a blended genetic relationship matrix, which is computed using both genomic and pedigree relationship matrices [124]. The use of ssGBLUP model increased the accuracy of genomic selection in many contexts and species compared with GBLUP model [125-128]. However, the increases in prediction accuracy from using ssGBLUP over GBLUP were not consistent among studied traits (Table 8). The inconsistency could be caused by several factors, including the size of the training population [129,130], the relationship between the training and validation population [121,131], the extent of LD [132], or the genetic architecture of the studied trait [110,132,133].

Based on the results of this study, different prediction models were suggested for different studied traits. Although the BLUP model showed slightly higher accuracy than the GBLUP and ssGBLUP models (Table 7) for ELISA-G, the noticeable higher prediction bias of the BLUP model over the GBLUP and ssGBLUP models (Table 8) cannot be ignored. In the case of ELISA-G, where the differences in prediction accuracy among different models were slight, ssGBLUP, which showed the lowest prediction bias, would be the most appropriate prediction model for the selection of ELISA-G. For the DOF, which had low heritability, although ssGBLUP showed the lowest prediction bias (Table 8), the BLUP model provided the best prediction accuracy for this trait (Table 7), which indicated the BLUP model would be the better prediction model for the EBV prediction for the DOF. However, genomic prediction models have the potential to increase the ability and accuracy of prediction if larger training population size and marker density could be applied in future studies. The ssGBLUP model seemed more suitable to obtain genomic predictions for the IAT and Varf on an experimental population as the highest prediction ability and accuracy were observed on the ssGBLUP model in the predictions for these two traits (Table 7).

Conclusion

In this study, GWAS identified 17, eight, and seven significant SNPs associated with ELISA-G, IAT, and DOF, respectively, whereas no significant SNP was detected for Varf. Candidate genes related to immune response were identified for ELISA-G and IAT, while genes associated with feed intake or appetite were identified for DOF. Among the evaluated prediction methods, ssGBLUP produced the highest prediction accuracies for IAT and Varf, whereas pedigree-based

BLUP produced the highest accuracies for ELISA-G and DOF. Thus, the most accurate prediction method differed among the studied AD-resilience traits.

In practical mink breeding programs, genomic information could be integrated with existing pedigree and phenotypic records rather than replacing current selection practices. Based on the present results, ssGBLUP may be particularly useful for genetic evaluation of IAT and Varf, whereas pedigree-based BLUP remains competitive for ELISA-G and DOF. As larger reference populations with both phenotypes and genotypes become available, genomic evaluation could be progressively incorporated into routine selection for AD resilience.

Methods

Animals and Phenotypes

This study was approved by the Dalhousie University Animal Care and Use Committee (certification#: 2018-009 and 2019-012). All mink used in this study were farmed following the Code of Practice for the Care and Handling of Farmed Mink guidelines from the Canada Mink Breeders Association [134]. All used animals in this study were euthanized by the farm technicians using carbon monoxide from a compressed gas cylinder based on the Code of Practice for the Care and Handling of Farmed Mink guidelines from the Canada Mink Breeders Association (ISBN 978-1-988793-24-5) [134]. A chamber concentration of at least 4% carbon monoxide was applied to induce rapid, irreversible loss of consciousness followed by prompt death with minimal discernible discomfort in the mink [134]. The death of the mink was confirmed by examining for cessation of vital signs, including the absence of all movement, lack of a heartbeat and breathing, fixed and dilated pupil, and absence of all reflexes [134].

In this study, 1,411 mink born between 2015 and 2020 from CCFAR at Dalhousie University, Faculty of Agriculture (Truro, Nova Scotia, Canada) were used. Mink were housed individually in single cages, and feed was distributed to each pen every day. The amounts of feed allocated to mink were regulated based on the leftover records to avoid unnecessary feed waste and meet the mink's appetite. A persistent breeding program was not implemented during the study years. In 2013, an outbreak of AD happened at CCFAR; its precise cause remained uncertain, but feed contamination with AMDV and interaction with infected wild animals were considered likely factors. The mink used in this study were the progeny of 192 sires and 370 dams. Pedigree information of 17 generations comprising 24,864 individuals was used.

The immune response of the studied mink to AD virus exposure was evaluated using ELISA-G (ranged from 0 to 7 with 1-point increments) and IAT (ranged from 0 to 4 with 1-point increments) based on established protocols described by Hu et al. [22]. Blood samples from the mink, which were annually collected in mid-November prior to selecting breeders and in mid-February before mating from 2015 to 2020, were sent to Middleton Veterinary Services (Nova Scotia, Canada) for ELISA-G testing and used to perform IAT tests at CCFAR. The feed-intake-related resilience of the studied mink to AD virus exposure was measured by computing the Varf and DOF. The Varf and DOF were computed using the daily feed-intake data (DFI), which were collected according to the established procedures outlined by Davoudi et al. [135], based on the methodology detailed by Putz et al. [136]. The Varf was measured through the calculation of the root mean square error from within-individual regression analysis, utilizing ordinary least squares linear regression, applied to DFI regressed on day. Identification of off-feed days involved a 5% quantile regression

of DFI against age (in days) for all studied individuals, with off-feed days for each mink being those exhibiting negative residuals below the regression line. Ultimately, the proportion of off-feed days to the total recorded days of DFI determined the DOF. Repeated daily feed intake records were available for each mink and were used to derive the feed-intake-related resilience traits as described previously [21]. Varf was calculated from the within-individual variation in daily feed intake, whereas DOF was calculated as the proportion of off-feed days; therefore, each animal had a single derived record for Varf and DOF. For AD test traits with repeated measurements, permanent environmental effects were tested and included in the model when significant, as described previously [21,22].

Sample Collection and Genotyping

The genotypic data of 1,411 mink used in this study were a subset of genotypic data from Hu et al. [137]. Briefly, the DNAs were extracted from the individual tongue tissues using the DNeasy Blood and Tissue Kit (Qiagen, Hilden, Germany) in accordance with the manufacturer's instructions. The NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies Inc., Wilmington, DE) was used to evaluate the quality and quantity of the extracted DNAs. The genotyping was performed using the Axiom Affymetrix Mink 70K panel (Neogen, Lincoln, Nebraska, USA) [50].

De-regressed Estimated Breeding Values for GWAS analyses

The individual EBV for all studied traits were obtained from the study by Hu et al. [21], where a univariate animal model was employed utilizing ASReml 4.1 software [138]. The obtained EBVs were transferred to the dEBVs using the formula:

$$dEBV = \frac{g_i}{r_i^2}, \quad [1]$$

where g_i is the EBV of the i^{th} individual and r_i^2 is the square of estimated accuracies for the i^{th} individual [139], using the DEBV calculator software [140]. Only the individuals, which had a reliability of dEBV more than 0.1 for at least one studied trait, were kept in the dataset for the following analyses. The derived dEBVs for each trait were utilized as pseudo-phenotypes to perform the following GWAS analyses.

Animal and SNP Quality Control

The SNP data and animals were filtered using PLINK [141] before conducting analyses. The SNPs, which had minor allele frequencies lower than 5%, call rates lower than 90%, excess of heterozygosities higher than 15%, and Mendelian error frequencies larger than 5% and were out of Hardy-Weinberg equilibrium with very low probability (1×10^{-6}), were excluded from the SNP dataset. The mink, which had reliability of dEBV less than 0.1 for all studied trait and call rates lower than 90%, were excluded from the dataset.

Genome-Wide Association Studies

A single SNP univariate mixed linear animal model was used to perform the GWAS using the snp1101 software [142]. The model is described as follows:

$$\mathbf{y} = \boldsymbol{\mu} + \mathbf{X}\mathbf{m} + \mathbf{W}\mathbf{a} + \mathbf{e},$$

where $\mathbf{y}$ is the vector of the dependent variable (dEBV); $\boldsymbol{\mu}$ is the population mean, $\mathbf{m}$ is the vector of the SNP marker effects; $\mathbf{a}$ is the vector of the residual polygenic effects with a normal distribution $\mathbf{a} \sim N(0, \mathbf{G}\sigma_a^2)$, where $\mathbf{G}$ is the realized relationship matrix constructed with markers [26], and σ_a^2 is the additive genetic variance; $\mathbf{e}$ is the vector of residual errors with a normal distribution $\mathbf{e} \sim N(0, \mathbf{I}\sigma_e^2)$, where $\mathbf{I}$ is an identity matrix, and σ_e^2 is the residual variance; and $\mathbf{X}$ and $\mathbf{W}$ are the incidence matrices of $\mathbf{y}$ and are related to $\mathbf{m}$ and $\mathbf{a}$, respectively.

The false-discovery rate (FDR) was employed as a correction to define the significant threshold [143]. The threshold p-value was calculated as $\mathbf{p} = \mathbf{FDR} * \frac{N}{M}$; the **FDR** was set to 0.01, N is the number of SNPs with p-value less than 0.01, and M refers to the total number of SNPs after quality control. The proportion of dEBV variance explained by significant SNPs was calculated according to the method proposed by Shim et al. [144]. Quantile-quantile (Q-Q) plots and genomic inflation factor [145] were applied to compare observed distributions of $-\log(\text{p-values})$ to its expected distributions under the no association model for each trait.

Gene Annotation, Gene Ontology, and Functional Analysis

The positional candidate genes within the range of the significant SNPs ± 350 kb region were annotated using the Bedtools software [146] referring to chromosome-level *Neogale vison* genome assembly ASM_NN_V1 (NCBI accession GCF_020171115.1)[147], which was annotated using the NCBI Eukaryotic Genome Annotation Pipeline. The delimitation of the regions was based on a previous investigation that indicated that linkage disequilibrium ($r^2 < 0.2$) within the present American mink population under study did not surpass 350 kb [137]. The process of assigning gene ontology (GO) terms, which includes biological process (GO:BP), cellular component (GO:CC), and molecular function (GO:MF), to annotated genes was carried out using PANTHER 14.1 [148]. The evaluation of the overrepresentation of annotated genes was performed through Fisher's exact test, and the FDR correction was used for adjustment. The terms with FDR-adjusted p-value (q) < 0.05 were considered significantly overrepresented. Additionally, the metabolic pathway analyses were conducted using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database and utilizing the clusterProfiler package [149] in the R program with a significant threshold of $q < 0.05$.

Statistical Methods for Genetic and Genomic Predictions

Traditional BLUP

Model 1 was applied to estimate the breeding values of each animal utilizing ASReml 4.1 software [138]. The model was as follows:

$$\text{Model 1. } \mathbf{y} = \mathbf{1}\mu + \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{a} + \mathbf{W}\mathbf{pe} + \mathbf{D}\mathbf{m} + \mathbf{e},$$

where $\mathbf{y}$ is the vector of phenotypes; μ is the overall mean; $\mathbf{X}$, $\mathbf{Z}$, $\mathbf{W}$, and $\mathbf{D}$ are the incidence matrix relating phenotypes to fixed, random additive genetic, random permanent environmental, and random maternal genetic effects, respectively; $\mathbf{b}$ is the vector of fixed effects (year, sex, age, color types, and cage location in the farm); $\mathbf{a}$ is the vector of random additive genetic effects, with $\mathbf{a} \sim N(0, \mathbf{A}\sigma_a^2)$, where $\mathbf{A}$ is the numerator relationship matrix, and σ_a^2 is the additive genetic variance; $\mathbf{pe}$ is the vector of random permanent environmental effects, with $\mathbf{pe} \sim N(0, \mathbf{I}\sigma_{pe}^2)$, where

I is an identity matrix, and σ_{pe}^2 is the permanent environmental variance; m is the vector of random maternal genetic effects, with $m \sim N(0, A\sigma_m^2)$, where σ_m^2 is the maternal genetic variance; and e is the vector of residual effects, with $e \sim N(0, I\sigma_e^2)$, where σ_e^2 is the residual variance.

Model 1 was previously tested and established for these traits [21,22]. Potential systematic and environmental effects were considered during model development, and the final model for each trait only included significant ($p < 0.05$) fixed effects and random effects. Therefore, the same established model was used in the present study without repeating the detailed model-selection procedures. The variance components of each trait (full dataset and cross-validation datasets) were estimated using ASReml 4.1 software [138] in BLUP model (**Model 1**).

Subsequently, the dEBVs were obtained using the same formula (equation [1]) and software stated in the previous genome-wide association analyses section. The dEBVs were used for the following genomic BLUP analyses.

Genomic BLUP

The computed dEBVs were used as the pseudo-phenotypes in GBLUP analyses, and the GBLUP method was performed using Model 2 implemented in SNP1101 software [150]. The model was as follows:

$$\text{Model 2. } y_c = 1\mu + Zg + e,$$

where y_c is the vector of dEBVs (training population) as pseudo-phenotypes; μ is the overall mean; Z is the incidence matrix relating pseudo-phenotypes (dEBVs) to GEBVs; g is the vector of GEBVs, with $g \sim N(0, G\sigma_g^2)$, where G is the genomic relationship matrix and σ_g^2 is genomic variance; and e is the vector of random residual effects, with $e \sim N(0, W\sigma_e^2)$, where W is a diagonal matrix of residual weights and σ_e^2 is the residual variance. The residual weights were calculated based on the reliability of dEBVs (r_i^2) using the approach described by Garrick et al. [139] as follows:

$$w = \frac{1 - r_i^2}{r_i^2}$$

The genomic relationship matrix (H) was computed based on the method proposed by VanRaden [26] as follows:

$$G = \frac{ZZ'}{2 \sum p_i(1 - p_i)},$$

where Z is a matrix of the centered SNP genotypes; Z' is a transpose matrix of M ; and p_i is the minor allele frequency of the i^{th} SNP.

The variance components of each trait were obtained by applying the “aireml” procedure of SNP1101 software in GBLUP model (**Model 2**).

Single-Step Genomic BLUP

The ssGBLUP analysis [124,151] was carried out using the program BLUPF90 [152]. Model 3 was used for the single-step genomic evaluation of each animal:

$$\textbf{Model 3. } \mathbf{y} = \mathbf{1}\mu + \mathbf{X}\mathbf{b} + \mathbf{Z}\mathbf{g} + \mathbf{W}\mathbf{pe} + \mathbf{D}\mathbf{m} + \mathbf{e}$$

where $\mathbf{y}$, μ , $\mathbf{X}$, $\mathbf{b}$, $\mathbf{W}$, $\mathbf{pe}$, $\mathbf{D}$, $\mathbf{m}$, and $\mathbf{e}$ were the same as parameters described in *Model 1*. $\mathbf{Z}$ is the incidence matrix relating phenotypes to GEBVs, and $\mathbf{g}$ is the vector of GEBVs, with $\mathbf{g} \sim N(\mathbf{0}, \mathbf{H}\sigma_g^2)$, where $\mathbf{H}$ is the relationship matrix, and σ_g^2 is the variance of genomic effects. The matrix $\mathbf{H}$ is a combination of relationship matrices using both marker genotypes ($\mathbf{G}$ matrix) and pedigree information ($\mathbf{A}$ matrix). The inverse of $\mathbf{H}$ matrix was obtained using the default option in BLUPF90 [152] as follows:

$$\mathbf{H}^{-1} = \mathbf{A}^{-1} + \begin{bmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \tau(\alpha\mathbf{G} + \beta\mathbf{A}_{22})^{-1} - \omega\mathbf{A}_{22}^{-1} \end{bmatrix}$$

where $\mathbf{A}_{22}$ is the pedigree-based relationship matrix of genotyped animals, τ and ω are the scaling factors, and α and β are blending factors of $\mathbf{G}$ and $\mathbf{A}$ matrices, respectively. The τ and ω were both set equal to one as the default option in BLUPF90 software [152]. The blending factors α and β were set equal to 0.95 and 0.05 as the default option in BLUPF90 software [152], respectively. The variance components of each trait were estimated from ssGBLUP model (*Model 3*) using the program BLUPF90 [152].

Cross-Validation and Model Comparison

The 5-fold cross-validation strategy was applied to different prediction models. The whole dataset was randomly partitioned into five subsets (folds), and each subset had approximately equal sample sizes (Table 9). Then, four subsets were used as training population to train the prediction model, and the remaining one subset was used for validation. At each repetition, cross-validation was performed in the group, which was not used in the training set. This scheme was repeated until each of the five subsets were used as the validation set. To account for sampling variation, splitting was repeated ten times.

The same training and validation populations were used for pedigree-based BLUP, GBLUP, and ssGBLUP. In each fold, the validation populations consisted of 224, 223, 177, and 177 mink for ELISA-G, IAT, DOF, and Varf, respectively, while the corresponding training populations consisted of 896, 891, 713, and 713 mink. Across the five folds, all 1,120, 1,114, 890, and 890 available animals, respectively, were included once in the validation population during each cross-validation repetition (Table 9).

The prediction accuracies obtained in this study should be interpreted as within-population cross-validation accuracies. Forward validation across generations was not performed because the available animals represented overlapping annual cohorts rather than clearly separated parental reference and offspring validation generations, and the recording periods differed among traits. In particular, DOF and Varf were recorded only in the later years of the study, which would have resulted in small and trait-specific parental reference populations. Future studies using larger, consistently phenotyped and genotyped populations with clearly defined generations are required to assess the persistence of prediction accuracy across generations.

Table 9. Number of animals in the training and validation populations.

Traits ¹	Total animals	Training animals	Validation animals
ELISA-G	1,120	896	224
IAT	1,114	891	223
DOF	890	713	177
Varf	890	713	177

¹ELISA-G=Aleutian mink disease virus antigen-based enzyme-linked immunosorbent assay test; CIEP=Counterimmunoelectrophoresis test; IAT=Iodine agglutination test; DOF=the proportion of off-feed days; Varf=Variation in daily feed intake; SD=Standard deviation; CV=Coefficient of variation.

To evaluate the prediction accuracy obtained with the different models, Pearson's correlations between the EBVs/GEBVs and the phenotypes adjusted for the fixed effects ($\mathbf{aY}$) were used [153]. The phenotype adjustment was performed using the *lm* function in R [154] and the complete dataset, which contained all phenotypic and genotypic information available in both validation and training subsets. This correlation is known as the prediction ability (r_{yy}) of the genomic selection to estimate phenotypes; therefore, the prediction accuracy (acc) is given by:

$$acc = \frac{r_{yy}}{h}$$

where r_{yy} is Pearson's correlation between the EBV/GEBV and $\mathbf{aY}$ (prediction ability), and h is the square root of the heritability estimated from using the full dataset for the studied trait (Varf and DOF) in the BLUP model (Model 1) or from our previous studies (ELISA-G, CIEP, and IAT) [21,22].

To evaluate the extent of prediction bias of prediction models, the regression of $\mathbf{aY}$ on the predicted breeding value (EBV or GEBV) was computed using simple linear regression of the adjusted phenotype on EBV/GEBV with an expected value of 1 for each trait.

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1144 **Availability of data and materials**

1145 The genotypic and phenotypic datasets generated and/or analyzed during the current study are
1146 subject to legal and institutional restrictions due to confidentiality agreements with the commercial
1147 data provider and therefore cannot be deposited in a public repository. The data may be made
1148 available from the corresponding author (YM) upon reasonable request and with permission from
1149 the data provider for the purpose of verifying the results of this study.

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1174 **Author contributions**

1175 M.S., G.P., Z.W., and Y.M.: conceived and designed the experiments. G.H.: performed the
1176 experiments and analyzed the data. G.H., D.N.D., G.M., A.A.K., and Y.M.: interpreted the results.
1177 G.H.: wrote the main manuscript. D.N.D.: collaborated in data preparations. Y.M.: supervised the
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1179 M.S., G.P., Z.W., and Y.M.: acquired the financial support for the project. All authors have read
1180 and agreed to the published version of the manuscript.

1181 **Competing interests**

The authors declare they have no competing interests. The funders had no role in the design of the study, data collection, data analyses, interpretation, writing of the manuscript, and the decision to publish the results. M.S. is employed by Select Sires Inc. This organization did not play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate

This study was approved by the Dalhousie University Animal Care and Use Committee (certification#: 2018-009 and 2019-012). All mink used in this study were farmed following the Code of Practice for the Care and Handling of Farmed Mink guidelines from the Canada Mink Breeders Association (ISBN 978-1-988793-24-5) [125]. The study is reported in compliance with the ARRIVE guidelines. In addition, we confirm that this research does not use any human tissue.

Supplementary Files

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