GENETIC AND PHENOTYPIC PARAMETERS FOR ALEUTIAN DISEASE TESTS AND THEIR CORRELATIONS WITH PELT QUALITY, REPRODUCTIVE PERFORMANCE, PACKED-CELL VOLUME, AND HARVEST LENGTH IN MINK

by

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ABSTRACT

The ineffective current methods in controlling Aleutian disease (AD) have urged mink farmers to select AD resilient mink based on some AD tests, however, little is known about their genetic and phenotypic parameters. In this thesis, we estimated the genetic and phenotypic parameters of four AD tests, including two systems of enzyme-linked immunosorbent assay (ELISA), counterimmunoelectrophoresis test (CIEP), and iodine agglutination test (IAT), and their genetic and phenotypic correlations with pelt quality, reproductive performance, packed-cell volume (PCV), and harvest length (HL). Estimated heritabilities (±SE) were 0.39±0.05, 0.61±0.07, 0.11±0.07, and 0.26±0.05 for antigen-based ELISA (ELISA-G), virus capsid protein-based ELISA, CIEP, and IAT, respectively. The ELISA-G had a moderate repeatability (0.58±0.04) and significant ($P<0.05$) negative genetic correlations (±SE) with reproductive performance traits (from -0.41±0.16 to -0.49±0.12), PCV (-0.53±0.09), and HL (-0.45±0.16). These results indicated that ELISA-G had the potential to be an indicator for genetic selection of AD resilient mink.

LIST OF ABBREVIATIONS AND SYMBOLS USED

%	Percent
AD	Aleutian disease
AMDV	Aleutian mink disease virus
AMDV-G	*in vitro* cultured Aleutian mink disease virus antigen
ASF	African swine fever
BL	Bluetongue
BLUP	Best linear unbiased prediction
BRDC	Bovine Respiratory Disease Complex
BVD	Bovine Viral Diarrhea
CAD	Canadian dollar
CCFAR	Canadian Centre for Fur Animal Research
CIEP	Counterimmunoelectrophoresis
cm	Centimeter
CV	Coefficient of variation
EBV	Estimated breeding value
ELISA	Enzyme-linked immunosorbent assay
ELISA-G	*in vitro* cultured Aleutian mink disease virus antigen-based enzyme-linked immunosorbent assay test
ELISA-P	Capsid protein of Aleutian mink disease virus-based enzyme-linked immunosorbent assay test
FISH	Fluorescence in situ hybridization
GBP	Pound sterling
GEBVs	Genomic estimated breeding values
GL	Gestation length
h^2	Heritability
HL	The body length at harvest age
IAT	Iodine agglutination test
IgG	Immunoglobulin G

JD	Johne’s disease
KTB	The number of kits born
KLB	The number of kits alive 24h after birth
KL3	The number of kits alive at 3 weeks of age
KLW	The number of kits alive at weaning age
MD	Marek's disease
NA	Not applicable
NAP	The grade of the nap length of fur at live grading
ND	Newcastle disease
NS	Not significant
NT	Not tested
PCR	Polymerase chain reaction
PCV	Packed cell volume
PRRS	Porcine reproductive and respiratory syndrome
QTL	Quantitative trait loci
QUA	The grade of fur quality at live grading
r^2	Repeatability
SD	Standard deviation
SNP	Single nucleotide polymorphism
SP	Sheep pox
USD	United States dollar
VP2	Capsid protein of Aleutian mink disease virus
σ_a^2	Additive genetic variance
σ_m^2	Maternal variance
σ_{pe}^2	Permanent environmental variance
σ_e^2	Residual variance

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CHAPTER 1 : GENERAL INTRODUCTION

1.1 INTRODUCTION

As the primary source of fur in the fur industries, American Mink (*Neovison vison*) farming is a high-financial return agricultural activity in Canada (Statistics Canada, 2018a, 2018b). The American mink is a semiaquatic and carnivorous mammal which belongs to the weasel (*Mustelidae*) family (García et al., 2010). American mink fur has been used as the major source of fur in the fur industries for many decades due to high-quality fur and various colors (Tamlin et al., 2009). From 2014 to 2018, the Canadian mink industry contributed about $96.41 million to the Canadian economy by producing approximately 2.68 million mink pelts each year (Statistics Canada, 2018a). As the largest mink producer province of Canada, Nova Scotia averagely produced over 1.46 million mink pelts and contributed about $47.78 million to the provincial economy each year from 2014 to 2018 (Statistics Canada, 2018a, 2018b). However, the severe economic losses caused by Aleutian disease (AD) and recently by severe acute respiratory coronavirus 2 (SARS-CoV-2) make it difficult for mink farmers to maintain their business.

Aleutian mink disease is an immune complex disease, which is induced by Aleutian mink disease virus (AMDV) infection, and cause some abnormalities including glomerulonephritis, arteritis, plasmacytosis, and hypergammaglobulinemia (Eklund et al., 1968; Ingram & Cho, 1974). The immune system of AD-infected mink is able to produce anti-AMDV antibodies, however, the produced antibodies cannot neutralize the virus but

rather form infectious virus-antibody complexes (Stolze & Kaaden, 1987). These infectious virus-antibody complexes have been found in the serum of infected mink (Porter & Larsen, 1967). The deposits of infectious virus-antibody complexes have been proved to cause the lesions in the glomerulus and arteries (Porter et al., 1969; Cho & Ingram, 1973; Porter et al., 1973). The significant economic losses to the mink industry are caused by serious anemia (McGuire et al., 1979), decreasing female reproductive performances (Henson et al., 1962; Reichert & Kostro, 2014), increasing high adult and embryonic mortalities (Henson et al., 1962), decreasing body size (Kowalczyk et al., 2019), and debasing pelt quality (Farid & Ferns, 2011). In Nova Scotia, AD causes multi-million-dollar economic losses to the mink industry (Rupasinghe & Farid, 2017).

Currently, no vaccine or treatment is available for this disease, and the main control method is the test-and-remove strategy, which culls the mink with positive AD tests result such as iodine agglutination test (IAT) and counterimmunoelectrophoresis (CIEP). Although the test-and-remove strategy has been used in many mink ranches in North America (Canada and US) and Europe (the Netherlands, Denmark, and Iceland) for over 30 years, AMDV has not been effectively eradicated from these ranches (Gunnarsson, 2001; Christensen et al., 2011; Themudo et al., 2011; Farid et al., 2012). The unsatisfactory outcome of the test-and-remove strategy has urged the fur industry to select for AD resilient mink.

Genetic selection for favorable health traits (e.g. disease tolerance, disease resilience, and immune response) provides a potential method for animal farming industries to cope with the adverse effects of diseases and control some untreatable farm animal diseases (Hu et al., 2020). It is undeniable that the traditional disease control methods such as vaccination, treatment, eradication strategy, and several other rising disease control and detection

methods such as genome editing, biosensor, and probiotics, are contributing to control the diseases in farm animals, however, the limitations and deficiencies of these methods cannot be ignored. These limitations and deficiencies drive animal breeders to be more concerned and committed to controlling diseases by selecting animals with improved health traits (Hu et al., 2020).

Some mink farms in North America and Europe select AD resilient mink based on the test level of gamma globulin or anti-AMDV antibody, as hypergammaglobulinemia is one of the typical symptoms of AD (Henson et al., 1962; Williams et al., 1965), and the high level of anti-AMDV antibody can form the infectious virus-antibody complexes and enhance the AMDV infection (Porter et al., 1972; Kanno et al., 1993; Bloom et al., 1994; Aasted et al., 1998; Bloom et al., 2001). A few mink farmers in Nova Scotia selected AD resilient mink based on the combination of animal health, production, and IAT results (Farid & Ferns, 2017). Some AD positive mink farms in North America and Europe are selecting AD resilient mink based on the enzyme-linked immunosorbent assay (ELISA) test, which is an AD-specific test used to identify and quantify the AMDV antibodies from mink sera samples (Knuuttila et al., 2009; Farid & Rupasinghe, 2016; Farid et al., 2018). The AMDV-G ELISA (ELISA-G), an antigen-based ELISA, and VP2 ELISA (ELISA-P), a virus capsid protein-based ELISA, systems are two main ELISA systems commonly employed in the mink industry (Farid & Rupasinghe, 2016).

Although some mink farmers have applied some AD tests in their farms to select AD-resilient mink, but the feasibility of this procedure has not been verified. Meanwhile, the estimation of genetic and phenotypic parameters for traits of interest are essential for animal breeders to design an effective genetic evaluation program (Safari et al., 2005), but

to the best of our knowledge, the genetic analysis of AD tests and their correlations with pelt quality, female reproductive performance, packed-cell volume (PCV, an indication of the extent of anemia), and harvest length traits have not been investigated in mink populations.

1.2 OBJECTIVES

This thesis, therefore, aimed to 1) estimate the heritabilities for four AD tests (ELISA-G, ELISA-P, CIEP, and IAT), 2) estimate the genetic and phenotypic correlations among AD tests, and 3) estimate the genetic and phenotypic correlations between AD tests and pelt quality, female reproductive performance, PCV, and harvest length traits in mink. The genetic and phenotypic parameters estimated in this thesis could help mink farmers to identify whether the AD tests could be applied as good indicator for selection of AD resilient mink. This information would also help mink farmers to implement a proper genetic selection program on their farms to cope with the adverse effects caused by AD.

CHAPTER 2 : LITERATURE REVIEW[1]

2.1 INTRODUCTION

Disease control is a global challenge for livestock industries and farmers, as diseases bring tremendous economic losses to farm animal production systems. The animal farming systems in both developed and developing countries are suffering economically from different infectious diseases. The direct economic losses from the outbreaks of disease can account for up to 20% of the revenue in developed countries and up to 50% of revenue within the livestock sector in the developing world (Bishop & Woolliams, 2014). Basically, all farm animal production systems are vulnerable to disease. Many diseases, such as bovine viral diarrhea (**BVD**), Johne's disease, and bovine respiratory disease complex (**BRDC**) in cattle farming; bluetongue and sheep pox in sheep farming; porcine reproductive and respiratory syndrome (**PRRS**), and African swine fever (**ASF**) in the swine industry; Newcastle disease and Marek's disease in the poultry industry; and Aleutian disease in the mink industry, contribute to economic losses and cause serious animal welfare issues via persistent infection, increased mortality, reduced productivity and reproduction performance, and decreased product quality. Therefore, finding effective solutions to combat diseases has become a top priority for all livestock industries.

To control diseases, many methods have been used with some level of success. Vaccination, medical treatment, and eradication strategy are three common methods to control health

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issues caused by diseases. These methods, however, are facing some bottlenecks, such as the side effects of vaccination (Yeruham et al., 2001; Rashid et al., 2009), the public concerns about residual drugs and drug resistance after employing medical treatment (Rokka et al., 2005; Ibrahim et al., 2010; Kehinde et al., 2012; de Jong et al., 2014; Beyene, 2016; Wilson, 2020), and the financial cost and high recurrence rate of using eradication strategies (Themudo et al., 2011; Pritchard et al., 2017a).

Several other methods, including genome editing, biosensor, and probiotics, provide animal farming industries more options to enhance animal health. Unfortunately, the lack of effective legal oversight (e.g., genome editing) and technological immaturity (e.g., genome editing, probiotics, and biosensor) make these technologies not widely available for controlling diseases of farm animals. This makes seeking alternative solutions one of the main concerns for animal producers.

Breeding for favorable health traits is one solution that is highly anticipated. Health traits mainly include health body traits, disease susceptibility traits, and immune system traits. Selecting favorable health traits, which are complex traits influenced by many genes and environmental factors, is a powerful tool against disease (Holmberg & Andersson-Eklund, 2004). Host genetics is significant in controlling the health status of each individual in the same environment. Compared with the other methods of disease control in farm animals, the selection of animals with favorable health traits, such as disease resistance, disease tolerance (Doeschl-Wilson et al., 2012), and immunity responses (Mallard et al., 2015), has many advantages. Classical genetic selection and genomic selection are playing important roles in genetically improving health and controlling diseases. Although many challenges exist in both selection methods, the great potential to genetically eradicate

diseases from farming systems is still attracting the attention of many animal farming industries.

Given the importance of disease in farm animals and the dramatic development of technologies for disease characterization, it is crucial to have a comprehensive and holistic view about challenges and solutions for combating disease in farm animals. Therefore, this chapter was written: (1) to present an overview of common diseases in farm animals and the methods used to control them; (2) to highlight the advantages of coping with diseases by selecting for health traits through genetic or genomic selection, as well as the current stages of selection on major diseases in livestock industries; and (3) to discuss the major challenges of employing health trait selection and the potential solutions that can help improve selection.

2.2 FARM ANIMAL DISEASES: INFLUENCE, PREVALENCE, AND CONTROLLING ISSUES

2.2.1 THE INFLUENCE, PREVALENCE, AND CONTROLLING ISSUES OF COMMON DISEASES IN FARM ANIMALS

Disease in farm animals is a significant challenge to farm animal industries worldwide. Cattle, sheep, swine, poultry, and fur-bearing animals, such as mink, are the most important farm animals for human society and provide the main resource of milk, meat, egg, wool, and fur. Unfortunately, all these important farming systems are vulnerable to disease (Figure 2.1).

In cattle, BVD, Johne's Disease, and BRDC are the most costly and persistent diseases (Table 2.1). The BVD commonly causes respiratory and reproductive complications in the

herd. The prevalence of BVD in Northern Ireland can reach as high as 98.5% in non-vaccinated dairy herds and 98.3% in beef herds (Cowley et al., 2014). The BVD causes the dairy industry to lose 40 to 100 thousand US dollars per herd in Canada and 10 to 40 million US dollars per million calvings in Europe (Carman et al., 1998; Houe, 2003). Culling infected animals and vaccinations are employed as short-term strategies to control this disease; however, they do not effectively eradicate BVD from the dairy farms (Brownlie, 2014; Pinior et al., 2017). Johne's disease affects the small intestine of ruminant animals and results in weight loss, diarrhea, decreased fertility, and death. The current strategy of controlling Johne's disease is based on timely detection through *Mycobacterium avium ssp*. *Paratuberculosis* enzyme-linked immunosorbent assay testing and then culling infected animals as there is no effective vaccine or treatment. For this reason, Johne's disease is still rampant worldwide (Pritchard et al., 2017a). Approximately 68% of dairy operations in the USA were affected by this disease (Attalla et al., 2010). This disease causes economic losses of 15 million Canadian dollars per year to the dairy industries in Canada, and 200 to 250 million US dollars per year in the USA (Cho et al., 2013). The BRDC, which is usually associated with infections of the lungs, causes pneumonia in calves and has been regarded as one of the primary causes of morbidity and mortality in beef farming (Miles, 2009; Gershwin et al., 2015). In the USA, BRDC is the leading natural cause of death in beef cattle and causes financial losses of more than one billion US dollars annually (Neibergs et al., 2014). The main method of controlling BRDC is using antibiotics; however, bacterial pathogen resistance to antibiotics for BRDC has caused the producers, practitioners, and the animal health industry to doubt the sustainability of using antibiotics to control BRDC (DeDonder & Apley, 2015).

In sheep, bluetongue and sheep pox are two common diseases in the sheep industry, causing significant economic losses (Table 2.1). Bluetongue causes huge economic losses to the sheep industry due to high mortality and morbidity, as well as the trading of animals associated with its outbreak. The prevalence of bluetongue was 19% in Italy (Carvelli et al., 2019), but in Sudan, the prevalence has been as high as 94% (Elhassan et al., 2014). In 2007, the cost of the bluetongue disease for sheep breeding farms in the Netherlands was estimated at 12.6 million euros (Velthuis et al., 2010). Vaccination has been regarded as the most viable method for the prevention and eradication of bluetongue disease; however, the expensive cost and potential side effects seriously influence the practicality and effectiveness of bluetongue disease vaccine (Kyriakis et al., 2015). Sheep pox is a serious, and often fatal, infectious disease in sheep and causes a high mortality rate in sheep populations. Although live vaccines have been developed and are used worldwide, sheep pox still persists in regions where vaccination is routinely practiced, causing huge economic losses to the sheep industry (Boumart et al., 2016). Up to 22% (Hota et al., 2018) and 40% (Hurisa et al., 2018) of sheep in India and Ethiopia were infected by this disease, respectively. Annual economic losses from sheep pox disease in Maharashtra, India, were 2.4 million US dollars due to high mortality rates (Garner et al., 2000).

In swine, outbreaks of contagious diseases, such as PRRS and ASF, have not only resulted in significant economic losses for swine industries but have also caused animal welfare and environmental concerns (Table 2.1). The disease, PRRS, can cause anorexia, lethargy, hyperemia of the skin, dyspnea, hyperthermia, increased mortality rates, and reduction in average daily gain (Lunney et al., 2016). Up to 48% of swine farms in Ontario, Canada, were infected by PRRS from 2010 to 2013 (Arruda et al., 2015). In 2013, the total annual

losses due to PRRS in the US were estimated at 664 million US dollars (Holtkamp et al., 2013). In Canada, the cost of PRRS was estimated at 130 million Canadian dollars per year (Mussell et al., 2011). Vaccination is considered the most feasible method for PRRS control; however, the high mutation rate and antigenic variability of the PRRS virus influences the effectiveness of controlling PRRS through vaccination. Meanwhile, the limited protection period of the vaccine against PRRS makes vaccination effective for only short time periods instead of eradicating the virus permanently (Hess et al., 2016; Sun et al., 2016). The ASF is a viral disease that leads to high morbidity and mortality in swine and has drastic influences on global domestic swine production. The absence of an effective vaccine and available methods of disease control causes tremendous economic losses to the infected areas (Brown & Bevins, 2018). The ASF was reported in most provinces of China from August 2018 to July 2019 and resulted in an insufficient supply of pork products in China. The overall mean rate of incidence was 12.5%, and the highest incidence rate of 30% occurred in April-May 2019 (Liu et al., 2019). In Russia, ASF has resulted in the loss of 800,000 pigs and 0.83–1.25 billion US dollars since its outbreak in 2007 (USDA, 2017).

In poultry, diseases, such as Newcastle disease and Marek's disease, cause devastating economic losses worldwide (Table 2.1). Newcastle disease was regarded as one of the biggest threats to the poultry industry, as this disease significantly affected poultry production throughout the world and has accounted for huge economic losses due to high mortality, high morbidity, and trade restrictions (Bello et al., 2018). The average prevalence in adult birds was 85% in the breeding and wintering grounds of Michigan, Mississippi, and Wisconsin states of the US and Ontario province of Canada, from 2009

to 2011 (Cross et al., 2013). The outbreak of Newcastle disease in California state of the US, from 2002 to 2003, caused 3.3 million birds to be culled and cost 200 million US dollars to eradicate the virus (Wise et al., 2004). With no effective treatment for Newcastle disease, vaccination is primarily used by the poultry industry to control the spread of disease. The multiple worldwide outbreaks of Newcastle disease in the past few years, however, have shown that the vaccination strategies are not fully effective in controlling this disease in different environmental conditions (Dimitrov et al., 2017; Mayers et al., 2017). Marek disease is another disease that affects the poultry industry and is one of the most ubiquitous highly contagious viral avian infections affecting chicken flocks worldwide. Although the clinical Marek disease is not always apparent in infected flocks, the subclinical decrease in growth rate and egg production can significantly affect the economic benefits of chicken farms (Morrow & Fehler, 2004). In Iraq, the overall prevalence of Marek disease was 49.5% with a range of 37% to 65% in different areas (Wajid et al., 2013). Even though mass vaccination is relatively efficient in controlling Marek's disease, the appearance of highly virulent strains that can decrease vaccine immunity results in Marek's disease virus continuing to cause a serious threat to the poultry industry (Boodhoo et al., 2016; Reddy et al., 2017). The annual economic losses due to Marek's disease were estimated as high as 1–2 billion US dollars worldwide (Dunn & Gimeno, 2013).

As the primary source of fur among all fur industries, mink farming also suffers from the serious economic losses caused by Aleutian disease (Table 2.1). Aleutian disease, a chronic and persistent viral infection, can cause a decrease in litter size (2.5 kits per whelping), high adult and embryonic mortalities (30–100%), and poor fur quality (Hansen & Lund,

1988; McDonald & Lariviere, 2001; Farid & Ferns, 2011; Reichert & Kostro, 2014). From 1998 to 2005, 24% to 71% of farmed mink were infected in Nova Scotia province of Canada (Farid et al., 2012). The test-and-remove strategy, which is the process used to remove mink tested positive for Aleutian Disease, is employed as the main method to control Aleutian disease because of the ineffective immunoprophylaxis and treatment (Farid et al., 2018). The unsatisfactory outcome of the test-and-remove strategy, however, makes Aleutian disease still a major problem and results in tremendous economic losses for the mink industry in North America and Europe (Christensen et al., 2011; Farid et al., 2012). The annual economic losses to the mink industry were estimated at approximately ten million US dollars in Denmark during 1984 (Aasted et al., 1998).

2.2.2 CURRENT METHODS TO CONTROL DISEASES IN FARM ANIMALS

Many disease-controlling methods are contributing to help farm animals cope with diseases. Vaccination, treatment, and test-based culling strategies are common approaches for the livestock industry to treat diseases and reduce the economic losses caused by subsequent health issues. Meanwhile, the development of genome editing, biosensor, and probiotics have provided more options for solving the economic and animal welfare issues caused by disease in animal farming systems. These methods have made great contributions to the control of diseases, but their deficiencies exposed in the application process cannot be ignored (Table 2.2).

2.2.2.1 VACCINATION

Vaccination has long been a key tool to reduce disease in livestock and maintain the health and welfare of livestock. Vaccines are contributing to preventing and mitigating many livestock diseases, (e.g., Johne's Disease and BRDC in cattle, bluetongue and sheeppox in sheep, PRRS in swine, and Newcastle disease and Marek's disease in poultry), which have complex, limited or no treatment options available, as well as reducing the use and misuse of antibiotics (Grubman & Baxt, 2004; Zientara et al., 2010; Bastida & Juste, 2011; Buchy et al., 2020). Vaccines play a significant role in preventing livestock diseases, but they also have some unsatisfactory side effects. First, vaccines are only administered to healthy subjects because they aim to prevent, not to treat. This means the vaccine can only protect the animal from disease, instead of eradication of disease (Chen, 1999). Second, vaccination may cause adverse reactions in vaccinated animals. This means a vaccine may cause some adverse side effects (e.g., anaphylaxis, decrease in production traits) to a recipient (Yeruham et al., 2001; Rashid et al., 2009). Third, mass vaccination campaigns can be very expensive and may be unprofitable for some livestock farmers (Tago et al., 2017). Meanwhile, not all animal diseases have corresponding vaccines that can be used to control the diseases, such as Aleutian disease in mink and ASF in swine (Table 2.1). For Aleutian disease in mink, several studies for producing an effective vaccine against AMDV ended with failure such as formalin inactivated AMDV vaccine (Porter et al., 1972), and several studies created partially effective protection such as vaccinating mink AMDV capsid proteins (Aasted et al., 1998), and NS1 AMDV gene (Castelruiz et al., 2005).

2.2.2.2 MEDICAL TREATMENTS

Medical treatment is one of the main typical treatments for coping with diseases in farm animals. Veterinary drugs not only play a crucial role in controlling the diseases-related risks but also make contributions to higher agricultural productivity and a steady livestock supply (Page & Gautier, 2012; Wang et al., 2018). The overall economic benefit can be increased by using the medical treatments because their applications can increase feed efficiency and performance (growth rate, egg production) for 1% to 15% more than animals that do not receive antibiotics or medical treatments (National Research Council, 1999). Although veterinary drugs have played an important role in the field of animal husbandry and agro-industry, the increasing occurrence of residues and resistance have become issues worldwide (Rokka et al., 2005; Ibrahim et al., 2010; Kehinde et al., 2012; de Jong et al., 2014; Beyene, 2016; Wilson, 2020). For Aleutian disease in mink, no effective treatment has been created for AD so far. Cyclophosphamide is an immunosuppressive drug that can temporarily protect mink from the gross and microscopic lesions of AD, but it also causes several side effects such as necrosis and depletion of lymphoid tissues (Cheema et al., 1972).

2.2.2.3 CULLING

Culling infected animals and carrying strict hygiene practices are also commonly applied to control many highly contagious and inextirpable diseases in farm animals by reducing the transmission of disease. High culling rate and cost of culling make it expensive to control some diseases by culling strategy. The overall annual culling rate of 590 randomly selected dairy herds from New Zealand for BVD was 23.1% in 2002, and the cull cost for

each cow was 324 US dollars (Heuer et al., 2007). About 200,000 pigs were culled from August to October of 2018 due to the outbreak of ASF in China. The direct damage from culling was estimated at about 37.8 million US dollars (Shao et al., 2018). For controlling PRRS in Vietnam, the government needs to provide a subsidy to encourage pig farmers to voluntarily cull infected pigs (Zhang et al., 2014). This strategy, however, still cannot eradicate some of the viruses in some cases, such as Aleutian disease in mink and Johne's disease in dairy cattle (Themudo et al., 2011; Pritchard et al., 2017a; Farid et al., 2018). Many potential reasons lead to the failure of culling strategies, such as the variability of the virus genome, the ineffectiveness of biosecurity failure, viral transmission from wild animals, and the persistent virus on the farms (Canuti et al., 2016; Farid et al., 2018; Kashtanov & Salnikova, 2018).

2.2.2.4 GENOME EDITING

Genome editing is a powerful technology that can precisely modify the genome of an organism. The main genome editing tools are zinc-finger nucleases, transcription activator-like effector nucleases, and CRISPR/Cas9, which have been successfully employed to many farm animal species including swine, cattle, sheep, and poultry to cope with diseases at affordable costs by creating farm animals with disease-resistant genes (Wu et al., 2015; Lillico et al., 2016; Whitworth et al., 2016; Ruan et al., 2017; Tait-Burkard et al., 2018; Kalds et al., 2019; Proudfoot et al., 2019; Van Eenennaam, 2019). There are clear opportunities, especially in cases where conventional control options have shown limited success. For PRRS, the *in vitro* research has shown that the macrophage surface protein *CD163* and specifically the scavenger receptor cysteine-rich domain 5 (**SRCR5**) of the

CD163 protein mediate entry of PRRS virus into the host cell (Van Gorp et al., 2010). Based on this information, a genome-edited pig with increased resistance to PRRS virus infection could be generated with a disruption to the *CD163* gene. The genome-edited pigs created by completely knocking out the *CD163* gene (Whitworth et al., 2016; Yang et al., 2018) or by removing only the SRCR5-encoding genome section (Burkard et al., 2017; Burkard et al., 2018) showed resistance to PRRS virus infection. However, such studies did not deliver the complete resistance observed in the pigs in which the endogenous *CD163* gene was edited.

The effectiveness of genome editing in disease control will be influenced by many factors, such as the proportion of gene-edited animals in the population and how these gene-edited animals are distributed within and across farms (Tait-Burkard et al., 2018). The disease-specific epidemiological models, however, are missing in helping with defining the exact proportion of gene-edited animals needed for each species/disease. Meanwhile, the limited shelf-life of genome editing needs to be considered. Genome editing shares the potential risk of vaccines, as the efficacy might be time-limited due to the emergence of escape mutants (Tait-Burkard et al., 2018). Especially for some RNA viruses with extremely high mutation rates, like the PRRS virus (Murtaugh et al., 2010), this concern is justified. So far, no legal regulations have been established to supervise genome-editing animals, and all previous examples are at a preliminary stage. This means that applying this technology to farm animal production still needs a large amount of research and comprehensive monitoring systems to ensure biosafety (Tait-Burkard et al., 2018). On the other hand, public concerns about genome-edited farm animal products are also a factor that cannot be

ignored, and directly determines whether genome-edited farm animal products have market value (Ruan et al., 2017).

2.2.2.5 BIOSENSOR

A biosensor is used to quantify physiological, immunological, and behavioral responses of farm animal species through detecting specific interaction results to a change in one or more physico-chemical properties, which include pH change, electron transfer, mass change, heat transfer, uptake or release of gases or specific ions (Velasco-Garcia & Mottram, 2003). This technology is applied in disease detection and isolation, and health monitoring in cattle, swine, and poultry (Luo et al., 2010; Schaefer et al., 2012; Neitzel et al., 2014; Ye et al., 2014; Montrose et al., 2015; Tarasov et al., 2016; Neethirajan et al., 2017). Although the biosensor can detect abundant precise data, the data is currently not being effectively transferred into practical information that could be used for the decision-making process in farm animal health management. At the same time, the lack of investment by individual farmers has also limited the widespread application and promotion of this technology (Neethirajan et al., 2017).

2.2.2.6 PROBIOTICS

The use of probiotics is also believed to have great potential to reduce the risk of the diseases of farm animals, especially intestinal diseases, and to replace the use of some antibiotics (Galyean & Eng, 1998; Reid & Friendship, 2002). Creating a bacterial competition using probiotics, which are live microorganisms that provide a health benefit

to the host when administered in adequate amounts, is a strategy to maintain health and prevent and treat infections in animals (Reid & Friendship, 2002). Many probiotic products are available for farm animals to improve their health and prevent them from disease (Corcionivoschi et al., 2010; Markowiak & Śliżewska, 2018; Roy et al., 2019). Lack of statistical analysis, unclear experimental protocols, lack of precise identification of microorganisms, and missing data related to the viability of the organisms make it difficult to assess the studies associated with probiotics based on earlier research (Rautray et al., 2011). Meanwhile, the lack of an appropriate government regulatory framework and safety studies slow the industrial exploitation of novel probiotic genera and delay the large-scale application of this technology in animal farming (Sanchez et al., 2017).

2.3 SELECTION FOR ANIMALS WITH FAVORABLE HEALTH TRAITS

2.3.1 HEALTH TRAITS IN FARM ANIMALS: DEFINITION, CLASSIFICATION, AND COMPONENTS

Historical emphasis on farm animal selective breeding programs were only focussed on profitability, and the most easily measured traits, such as milk yield in dairy cows or bodyweight in swine. Recently, selection between and within breeds for health traits is attracting more attention from farm animal producers. The farmers realize that only by having a more comprehensive assessment of animal performance can the level of productivity be maintained or improved (Haskell et al., 2014).

Health traits could simply be the traits related to the health status of animals, and therefore, they could be disease traits or host immune status. According to the Animal Trait Ontology

(Hughes et al., 2008; Golik et al., 2012), health traits are a part of animal welfare traits. The traits could be further divided into three main groups, including health body traits, disease susceptibility traits, and immune system traits. For each group, several subgroups are also included, such as immune system traits which could include acquired immune system traits and innate immune systems traits. Health traits are defined by the interaction between host genetics and environment which includes the management factors as well as the pathogens. Host genetics play important roles in animals, which decide the health status of each individual in the same environment. Selection for host genetics often involves selection for disease resistance or tolerance as well as their immune systems. To maximize the host genetic potentials, it is important to study the gene by environment interaction. Genomic selection for gene by environment interaction might become more feasible using the big data (Mulder, 2017).

Health traits could be reported at different levels as within (individual variations) or between populations. The heritabilities of health traits depend on many factors, such as the nature of the traits or the method of records; however, they are known to be low-to-moderate. For instance, the estimated heritabilities for the susceptibility of cattle to Johne's disease infection ranged from 0.06 to 0.18 (Koets et al., 2000; Mortensen et al., 2004; Gonda et al., 2006). Therefore, selection for health traits can be achieved but might require quite longer time compared to the other production traits with higher heritabilities.

2.3.2 THE BENEFITS OF SELECTING FARM ANIMALS WITH FAVORABLE HEALTH TRAITS

Genetic improvement of animal health brings many benefits to the farmers, such as increase in production, reduction in the cost of disease treatment, enhancement of product quality and fertility (Figure 2.2). Overall, it improves animal welfare as less animals suffer from disease, as well as improving environmental health and human health by reducing the potential disease transmission to humans. Breeding animals with health traits for controlling disease offers several advantages over the other methods of disease control. Selecting health traits, such as disease tolerance, disease resistance, and immune response, can be an inexpensive and relatively simple way to improve animal health, welfare, and productivity. Breeding for health traits appears more and more attractive as the infectious organisms evolve resistance to the drugs and vaccines used to control them, as the costs of treatment and veterinary care increases faster than the value of the animals, and as a result of the huge economic loss caused by the culling of animals with positive disease tests results.

Protecting farm animals by vaccination or drug treatment has been the major method used to protect at-risk farm animals; however, the public concern about vaccination or drug treatment is increasing due to the drug residues and the resistance of pathogens and parasites to drugs and vaccines (Morris, 2007). The intense selection pressure, which evolved into the resistance of parasites to drugs, can be imposed on the parasite population by treating farm animals with drugs, such as antibiotics or anthelmintics (Nicholas, 1987). Genetic improvement of the health of farm animals through selecting disease resistance may reduce the need for treatment with antibiotics and reduce the risk of residues in farm

animal products. The worldwide control strategies to cope with helminths are entirely based on the frequent use of dewormers, which are anthelmintic drugs (McManus et al., 2014). These control strategies have been increasingly regarded as unsustainable given the emergence of multiple drug-resistant parasites (Kaplan, 2004). Each time an anthelmintic is employed, the resistant parasites will be selected for and will pass their resistant genes onto the next generation of worms (McManus et al., 2014). As a result, breeding for genetic resistance is a significant component in integrated parasite management programs (Sayers & Sweeney, 2005). The genome-wide selection strategies are playing an important role in selecting animals for nematodes resistance traits (McManus et al., 2014). The most frequent reason for using antibiotics in lactating dairy cattle is mastitis (Guterbock et al., 1993). In the earlier research of bovine mastitis in Finland, the proportion of coagulase-negative *Staphylococci* resistant to at least one antibiotic drug increased from 27% in 1988 to 50% in 1995 and from 37% to 64% for *staphylococcus* strains (Myllys et al., 1998). Significant increases in the antibiotics resistance were also observed in France as tetracycline resistance in *Streptococcus uberis* isolates increased from 15.7% to 20.4% and third-generation cephalosporin resistance in *Escherichia coli* isolates increased from 0.4% to 2.4% in the period from 2006 to 2016 (Boireau et al., 2018). The issues of antibiotic resistance make a permanent improvement in mastitis resistance for cow through selected breeding even more important (Heringstad et al., 2000). Vaccination can be regarded as an alternative strategy for genetic improvement for mastitis; however, a single vaccination can only provide a short-term protection instead of a permanent protection from generation to generation. Although it may be more cost-effective in the short run by using effective low-cost vaccination, genetic improvement in disease resistance has more advantages in the long run (Heringstad et al., 2000).

Selection for health traits can reduce the production costs associated with disease control in farm animals (Gibson & Bishop, 2005). Culling, or the test-and-remove strategy, is one of the common approaches to control highly contagious diseases, such as PRRS in swine and Aleutian disease in mink. It can cause huge economic loss to farmers due to the expensive cost in replacing a diseased animal and the loss of farmed animals. Bovine tuberculosis, caused by the bacterium *Mycobacterium bovis*, is an endemic disease with zoonotic potential in many parts of the world, notably in the UK and Ireland (Bishop & Woolliams, 2014). The primary method used to control this disease is compulsory testing of cattle followed by the slaughter of test-positive animals, at a total cost exceeding GBP 227 million in the UK and Ireland in 2010–2011 (Abernethy et al., 2013). Highly tolerant animals still have good performance in an environment with significant virus exposure, and thus genetic selection for disease tolerance has the potential to reduce the production costs associated with culling diseased animals and eliminating the disease virus. In some developing countries, the majority of poor farmers cannot afford or do not have access to therapeutic and vaccine control, and thus the selection for healthy animals is critical for effective disease control (Gibson & Bishop, 2005).

Selection for animals with health traits (e.g., disease tolerance and disease resistance) has the potentials to bring positive economic impacts to animal farming industries. The disease-resistant animal has the ability to prevent the entry of a pathogen or inhibit the replication of the pathogen (Råberg et al., 2009). Therefore, selecting the disease-resistant animal has the potential to save the cost of medicine treatment and eliminate the economic losses caused by disease (such as reduced production, high mortality, and low fertility). The disease-tolerant animal has the ability to limit the influence of infection on its health

or production performance (Råberg et al., 2009). Hence, selecting the disease-tolerant animal has the potential to minimize the adverse influence caused by disease during the production period.

2.3.3 METHODS OF SELECTION FOR HEALTH TRAITS

Artificial selection is the process used for determining the parents for the breeding program, the number of offspring the selected parents produce, and the duration that the selected parents remain in the breeding population (Bourdon, 2014). Artificial selection is commonly used in farm animal selection to maximize the benefits by selecting favorable characteristics and excluding the features that are not sought after by the market. The principle of selection is choosing the individuals with the best sets of alleles as genetic parents to reproduce so that the next generation has more desirable alleles than the current generation. The consequence of successful selection is genetically improving future generations of a population by increasing the proportion of desirable genes in the population over time (Bourdon, 2014). The progress of selection for farm animal species can be viewed according to the development of molecular techniques as traditional genetic selection, marker-assisted selection and genomic selection.

2.3.3.1 TRADITIONAL GENETIC SELECTION

Improvement of farm animals has focused on the selective breeding of individuals with superior phenotypes. With the development of increasingly advanced statistical methods that maximize selection for genetic gain, this simple approach has been spectacularly

successful in increasing the quantity of agricultural output. Selections for certain health traits have been done for a long time when the ancient people tried to select animals with better health or resistance to certain diseases during domestication (Hart, 2011). These selections were purely based on their observation of performance characteristics without any information about molecular genetics. Existing selection techniques, however, still rely on laborious and time-consuming progeny-testing programs and often depend on subjective assessment of the phenotype. The traditional genetic selection breeding program evaluates the genetic potential of animals, which is based on breeding value, for some important traits using phenotype and pedigree information observed on the animal (Weigel et al., 2017). Genetic selection has significantly increased the production levels of farm animal species. The high accuracy of breeding value estimation, the moderate-to-high heritability of most production traits, and the use of large databases containing production records of many farm animal species and their genetic relationships have been found to boost breeding programs based on genetic selection and have become quite successful (Rauw et al., 1998). The application of genetic selection in commercial farm animals based on aspects of output, such as higher growth rate in poultry, less fat percentage rate in swine, and greater milk yield in cows, has had significant effects on outputs in the farm animal industries (Emmans & Kyriazakis, 2001). Genetic selection for health traits has been applied in countries with routine health data records collected for a long time. For instance, health traits have been included in breeding programs in Scandinavian countries since the mid-1970s (Heringstad & Østerås, 2013). Mastitis, ketosis and displaced abomasum diseases records were included in the breeding programs of dairy cattle in Canada (Miglior et al., 2014; Beavers & VanDoormal, 2016). The impacts of genetic selection for health traits depend on the nature of the traits (heritability), sample size, methods of recording,

the priority of selection (e.g., economic weight in the selection index), environments and species; however, the progress for genetic selection for health traits is often lower than production traits.

2.3.3.2 MARKER-ASSISTED SELECTION

The molecular techniques, such as Polymerase Chain Reaction (PCR), Fluorescence In Situ Hybridization (FISH), and Sanger sequencing, were developed in the 1980s (Durmaz et al., 2015). These techniques performed the amplification and sequencing of DNA and identification of markers linked to genes for economically important traits such as disease resistance. When available, these markers will provide animal breeders with an objective test system to identify the animals carrying desirable alleles at birth or even earlier, such as an embryo or sperm (Gogolin-Ewens et al., 1990). The method allows the identification of genes or DNA markers for genetically engineering disease resistance and selection of enhanced production traits (Gogolin-Ewens et al., 1990). Quantitative trait loci (**QTL**) mapping is the first step to detect chromosomal regions affecting complex traits, which will be used in the fine mapping for identification of DNA markers for traits of interest. The QTL detection experiments in farm animals started in the 1990s when Andersson et al. (Andersson et al., 1994) detected a QTL for fatness on chromosome four in pigs. Many QTLs were detected initially using initial linkage maps in either crossbreeds for highly divergent traits of interest, or commercial populations where half-sib families were available. In the early 1990s, QTL experiments were based on resource populations with a few hundred animals; over time resource population size has increased to thousands of animals coupled with an increasingly large number of markers. Consequently, the number

of detected QTL has also increased rapidly in different farm animal species (Table 3). While genetic markers that are linked to the QTL could be used to choose animals for selective breeding programs, the most effective markers are the functional mutations within the trait genes. For instance, the QTL identified for milk yields and components in chromosome 14 of Holstein dairy cattle is linked to the Acyl-CoA: Diacylglycerol Acyltransferase 1 (**DGAT1**) K232A Polymorphism in Holstein breed in Sweden (Näslund et al., 2008), Germany (Thaller et al., 2003), Canada (Do et al., 2020), and China (Jiang et al., 2010). Strategies to identify markers for traits and the application of these markers are described with reference to examples of loci that control a range of different traits (Williams, 2005). Detection of QTLs, and genes involving the traits of interest, helps to develop the marker-assisted selection programs (Wakchaure et al., 2015). For example, Ruane and Colleau (1996) found that the application of marker-assisted selection could increase 6% to 15% of the selection response for milk production in cattle that used multiple ovulation and embryo transfer in the first six generations of selection. However, most of the detected genes and markers only explain a small proportion of phenotypic variances, and therefore, they are not effective for the selection of quantitative traits. For instance, all genetic markers of 42k genotyping panel could only explain about 11% of phenotypic variation in mortality due to Marek's disease virus infection in layers (Wolc et al., 2013).

2.3.3.3 GENOMIC SELECTION

High-throughput genomic technologies, especially high-throughput single nucleotide polymorphism (**SNP**) genotyping, genotype-by-sequencing, as well as the whole genome

sequencing methods, have been commercially available for more than ten years. Genomic prediction/selection was the biggest change in the artificial selection of livestock species by adapting high-throughput genotyping technologies in the farm animal sector (Meuwissen et al., 2001). Genomic selection refers to making breeding decisions based on genomic estimated breeding values (**GEBVs**) obtained from SNP effects based on some prediction methods (Meuwissen et al., 2001). The main approach for genomic selection is to determine the SNP effects from a reference population consisting of a subset of animals with both SNP genotypes and phenotypes for traits of interest, then to use the SNP effects to compute the breeding values (genetic merit) for other genotyped animals that are not yet phenotyped. The basic statistical method used for genomic prediction is similar to the traditional best linear unbiased prediction (**BLUP**) method that has traditionally been used in animal breeding for a long time, except that the relationship matrix is computed based on SNP genotypes or genomic information. The major advantages of genomic selection are the higher prediction accuracy (compared to traditional EBVs obtained using pedigree information) and shorter generation interval (Piccoli et al., 2018). The accuracy of GEBVs depends on the size of the reference population used to derive prediction equations, the heritability of the trait, the extent of relationships between selection candidates and the reference population, the relationship between test and reference populations, number of SNPs, number of loci affecting the traits as well as how close assumptions in genomic prediction methods are to the truth (Goddard et al., 2010; Miar et al., 2015). Genomic selection has been successfully applied in the farm animal sections and has accelerated the genetic gain not only for the production traits but also for many health traits (Meuwissen et al., 2013).

2.3.4 SELECTION FOR DIFFERENT TYPES OF HEALTH TRAITS

2.3.4.1 SELECTION FOR DISEASE RESPONSE TRAITS (RESISTANCE, TOLERANCE, AND RESILIENCE)

Disease tolerance and resistance are the most common targeted disease response traits in farm animal breeding programs, as they are two natural and distinct mechanisms of a host's response to infectious pathogens and could be targeted for genetic improvement (Doeschl-Wilson & Kyriazakis, 2012). Resistance is the ability of a host to prevent the entry of a pathogen or inhibit the replication of the pathogen. Tolerance is an ability of a host to limit the influence of an infection on the host's health or production performance without interfering with the life cycle of the pathogen (Råberg et al., 2009).

To date, most efforts to control infectious disease focus on selecting disease resistance farm animals to improve the ability of the host to fight disease. The heritable differences of disease resistance between animals lead to opportunities to breed animals for enhanced resistance to the disease (Bishop & Morris, 2007). In cattle, the major focus on health traits selection is for mastitis resistance. Many different approaches have been proposed in order to increase the possibility of selection for mastitis resistance (Martin et al., 2018). Up to date, 2401 QTLs have been identified for mastitis resistance in dairy cows (Animal QTL Database. Available online: https://www.animalgenome.org/cgi-bin/QTLdb/BT/nscape?isID=1439, assessed on 20 February 2021). Not only increasing the number of QTL, the genetic and genomic selection for mastitis has also achieved a certain level of success (reviewed by Weigel and Shook (2018)) due to the increasing

accuracy of prediction for mastitis or the inclusion of different new methods of identification of mastitis incidence in the selection index. For instance, the accuracy of genomic prediction could reach as high as 0.50 to 0.55 for mastitis infection depending on the models (Fang et al., 2017). Unlike mastitis, less progress is reported for selection for Johne's disease and BRDC resistance, which might be due to the lack of accurate measurements and their less serious impact on production. The heritabilities for Johne's disease (range from 0.07 to 0.16) and BRDC (range from 0.07 to 0.19) resistance and differences among breeds have been documented in the previous studies (Snowder et al., 2005; Gonda et al., 2006; Attalla et al., 2010; Schneider et al., 2010). These heritability estimates and significant estimates of additive genetic variances indicate that computing traditional phenotype-based genetic evaluations for resistance to Johne's disease and BRDC is feasible in cattle populations. In swine, 43 QTLs for PRRS resistance have been mapped to 12 chromosomes (Animal QTL Database. Available online: https://www.animalgenome.org/cgi-bin/ QTLdb/SS/traitmap?trait_ID=779, assessed on 20 February 2021). The major QTL region was located on chromosome four (**SSC4**) that explained 16% of the genetic variance of PRRS virus load with a frequency for the favorable allele of 0.16 and a heritability of 0.30 (Boddicker et al., 2012). In poultry, a number of QTLs associated with Marek's disease resistance have been reported in various lines and breeds of chicken using SNP or microsatellite markers since 1998 (Vallejo et al., 1998; Yonash et al., 1999; McElroy et al., 2005; Cheng et al., 2008; Heifetz et al., 2009).

The research focus associated with selecting health traits has expanded to increase the host's tolerance to reduce the harmful effects of infection on health and performance (Doeschl-Wilson & Kyriazakis, 2012; Medzhitov et al., 2012). Genetic selections of

disease tolerance are rare, as the genetics of disease tolerance and its measurement are more difficult to elucidate than disease resistance in farm animals (Bishop & Woolliams, 2014; Lough et al., 2017). Growing evidence, however, indicates the potential for genomic selection of disease tolerance. Genomic studies have been able to map the QTL for tolerance traits as Zanella et al. (2011) identified a number of QTLs for Johne's disease and Hanotte et al. (2003) detected 16 QTLs for trypanosomosis, in the cross of N'Dama and Boran cattle. Meanwhile, the results of genomic prediction (accuracy of 0.38) for facial eczema suggested that genomic selection for the facial eczema disease tolerance has the potential to help the New Zealand sheep industry to cope with the issues caused by facial eczema (Phua et al., 2014).

Although both resistance and tolerance traits may be under genetic control and could thus be targeted for genetic improvement, selecting tolerance for disease may have some advantages over selecting disease resistance (Lough et al., 2017). Firstly, the resistance ability of a host can limit the replication of a pathogen within the host, and therefore, selecting host resistance has a potential to increase the selection advantages on pathogen strains that can withstand host resistance mechanisms and eventually result in a loss of selection advantage of the host (Roy & Kirchner, 2000; Restif & Koella, 2004). It is the potential pitfall for a long-term breeding strategy which focuses on disease resistance, if the disease virus has a high mutation rate, such as the PRRS virus in swine (Drake & Holland, 1999). It has been theoretically proposed that selecting tolerance might not motivate such selection pressure on the pathogen (Roy & Kirchner, 2000). Secondly, compared with the resistance mechanisms which directly influence the life-cycle of the pathogen, improving host tolerance has the potential to provide cross-protection against

other strains of the virus, or other prevalent infectious agents due to the mechanisms of tolerance which primarily target host-intrinsic damage prevention or repair mechanisms (Raberg et al., 2007; Ayres & Schneider, 2012; Medzhitov et al., 2012).

Resilience is another health trait that is attracting the attention of animal breeders. Generally, resilience is an ability of an animal either to minimize the influences caused by disturbances or to return to the body condition prior to exposure of a disturbance (Colditz & Hine, 2016). The capability of taking care of a larger number of animals is one of the requirements for the intensification of farm animal production. Selecting resilient animals can improve this capability of the farm animal industries because resilient animals are healthy and easy-to-care-for animals that need less attention time (Elgersma et al., 2018). On the other hand, compared to the direct selection based on disease tolerance and resistance, the selection based on resilience is a more pragmatic way of keeping healthy animals, because it does not need the records on pathogen burden, which is the amount of pathogen in the animal's body (Albers et al., 1987; Bisset & Morris, 1996; Mulder & Rashidi, 2017). Resilience, however, is not yet included in breeding goals due to the difficulty of phenotyping the traits (Doeschl-Wilson & Kyriazakis, 2012). Fortunately, the current developments on the big data collection and the new disease resilience indicators defined based on these data provide great opportunities to breed for improved resilience in livestock (Berghof et al., 2019).

2.3.4.2 SELECTIONS FOR IMMUNE RESPONSE TRAITS

Immunity response traits are also important health traits for animal breeders to select for improving the farm animals' ability to withstand disease. The immune system is important

to control infections and diseases. The immune response traits have been recommended to be selected for decreasing the incidence and impact of the disease in farm animals (Abdel-Azim et al., 2005; Mallard et al., 2015). In Holstein cattle, the lower occurrence of mastitis improved response to the commercial vaccine, and increased milk and colostrum quality are all observed in cows with superior or high immunity response (Rautray et al., 2011). Consequently, improving the inherent ability to cope with the diseases in dairy cattle through genetic selection for superior or high immunity response is feasible (Thompson-Crispi et al., 2012). In cattle, the High Immune Response (HIR™) and the Immunity+, which are used to identify and select animals with naturally optimized immune responses, have been applied in the genetic selection of cattle for improved immunity and health (Mallard et al., 2015). In swine, the total and differential numbers of leukocytes, expression levels of swine leukocyte antigens I and II, and serum concentrations of IgG and haptoglobin are immunity traits that have been demonstrated to have additive genetic variation. These immunity traits, therefore, have the potential to be used as criteria to improve the selection of pigs for coping with clinical and subclinical diseases (Henryon et al., 2006). In poultry, the presence of genetic variability in immune response traits and the discovery of SNPs associated with immune response traits indicate that genetically enhancing antibody response and resistance to parasitism is feasible through genomic selection (Psifidi et al., 2016). In mink, seven key genes including *TRAF3IP2*, *WDR7*, *SWAP70*, *TNFRSF11A*, *CBFB*, *IGF2R*, and *GPR65*, were identified to be related to immune system process with important roles in regulating the immune-mediated responses to AMDV infection (Karimi et al., 2021a).

2.3.5 CHALLENGES IN THE SELECTION OF HEALTH TRAITS

Health traits, such as disease resistance, disease tolerance, and immunity response level, are usually quantitative traits which are influenced by many genetic and environmental factors. Although genetic selection has significantly increased the production traits in farm animal species, such as higher growth rate, less fatness, and greater milk yield (Emmans & Kyriazakis, 2001), the selection for health traits is much more complicated and faces some challenging obstacles. The potential problems in selection for health traits can be classified under desirability, feasibility and sustainability (Stear et al., 2001).

2.3.5.1 DESIRABILITY

The desirability describes the importance of the disease relative to other diseases or production traits. The correlations between health traits and economic traits are often negative, which means the health traits are potentially genetically antagonistic to production traits (Schulman et al., 2004; Jie & Liu, 2011). Milk yield in dairy cattle has unfavorable correlations with many disease response traits (Simianer et al., 1991; Van Dorp et al., 1998). The genetic correlations between mastitis and milk production or high somatic cell score, which is the most widely used indicator of udder health in cow (Persson & Olofsson, 2011), and milk production are moderate and positive (Emanuelson, 1988). In poultry, genetic selection for greater body weight can lead to decreased immunity to fowl cholera and Newcastle disease (Li et al., 2001). The opposite results, however, also occur in some research. For example, van der Most et al. (2011) stated that selection for growth in poultry can compromise the immune function, while the selection for immune

function does not consistently affect growth. Identifying the genetic correlations between health traits and production traits in farm animals is, therefore, an important aspect of health traits selection. Applying the economic selection index is one of the solutions to deal with the antagonistic genetic correlation between traits. In 1943, Hazel (1943) first presented the aggregate genotype, which was also called net merit, of animals as a linear combination of breeding values for each trait weighted by the economic value of the traits. Subsequence, the economic selection index for multi-trait selection has been used in animal breeding research fields and employed in animal agriculture industries. The breeding objective can be defined as the aggregate breeding value expressed by profit or economic efficiency, and it is the overall goal of breeding programs to increase the profits or economic efficiency for breeders and/or producers. In this way, multi-trait selection with the economic selection index can minimize the adverse influences caused by the antagonistic genetic correlations between target traits to achieve the overall goal of breeding programs (Hirooka, 2019).

2.3.5.2 FEASIBILITY

Feasibility accounts for the tools available with which to perform the selection. The success of selection for health traits is highly dependent on correctly identifying the phenotype for traits associated with the host's abilities to withstand infectious diseases. Accurately identifying the phenotypes for health traits is expensive and difficult. An extensive data recording is required to enable an accurate genetic evaluation. High labor costs are required for long-term recording of large amounts of phenotypic and progeny data (Rashid et al., 2009). In a combined population of infected and healthy individuals, it is not correct to

consider an individual with good performance to have favorable health traits, nor the sick populations to be genetically susceptible (Snowder, 2006). Some susceptible animals still show good performance because they may not have been sufficiently exposed to the pathogens. An animal displaying a healthy performance without clinical symptoms may have sub-clinical infections and represents a pathogen carrier. The clinical expression of a disease can be confounded by infection with one or more similar diseases, such as pneumonia which can be confused with pulmonary adenomatosis, bronchitis, and pleuritis. Meanwhile, diagnosing a disease accurately and specifically is costly and time-consuming (Jie & Liu, 2011).

2.3.5.3 SUSTAINABILITY

Sustainability means the enhanced resistance to the infectious disease in the farms or flocks is stable for a long period, especially when the pathogens often evolve faster than the hosts (Stear et al., 2001). The long-term success of selection involves not only the choice of the best animals with disease resistance but also the management systems with the ability to cope with the constant changes in the farming environment. For instance, hot environment caused by global warming could impair production and reproductive performance, metabolic and health status, and immune response (Nardone et al., 2010). The climate changes also cause changes in the pathogens or create novel pathogens which require the producers to constantly adapt new methods and treatments for their animals. Genomic selection of robustness and fitness traits could be a solution for this challenge (Meuwissen et al., 2016; Berghof et al., 2019).

2.3.6 PROMISE OF SELECTION FOR HEALTH TRAITS

2.3.6.1 HIGH THROUGHPUT PHENOTYPING AND SEQUENCING, AND GENERATION OF BIG DATA

Big data is a mix of different sources of data (structured and unstructured) that comprises a large volume of information (Asokan & Asokan, 2015). The major characteristics of big data include volume, velocity, variety, variability, veracity, validity, and volatility (Normandeau, 2013). Big data has been adapted to the farm animal sector, such as precision farming (Berckmans, 2017), biosensors (Ip et al., 2018), electronic feeding stations, and automatic milking systems (Mulder, 2017). Big data is also important for infectious disease surveillance and modeling (Bansal et al., 2016; Berghof et al., 2019). It is clear that big data generated from high throughput phenotyping will give unprecedented opportunities for combating diseases and selecting healthy animals (Koltes et al., 2019; Rexroad et al., 2019). For example, mastitis and claw health can be recorded via high throughput phenotyping devices such as real-time biosensors (Halachmi et al., 2019; Khatun et al., 2020). The use of big data for animal health care, however, needs a careful handling of the data (Cole et al., 2020) and the selection of appropriate statistical methods (Morota et al., 2018; Morota et al., 2019). High-throughput sequencing data, such as genomics, transcriptomics, proteomics, and epigenomics etc., have been adapted to improve animal health (Suravajhala et al., 2016; Ibeagha-Awemu et al., 2018) as they could help to understand the biology of disease, computing EBVs, and pinpointing the biomarkers.

2.3.6.2 DATA SHARING AND INTERNATIONAL CORPORATIONS

Data sharing and international corporations can play crucial roles in the selection of healthy traits, even those selections that take place locally. The major reason for this is that many diseases in farm animals are transboundary diseases. The outbreaks of diseases could potentially affect other farms in different countries, such as the outbreaks of Avian Influenzas Virus that cause significant loss in many nations worldwide. Information sharing plays a crucial role in controlling diseases for nations on the same continent, especially for developing countries (Ibeagha-Awemu et al., 2019). It is also important to have a standard protocol for recoding the incidences, progress of the disease and consequences of diseases for better use of data. In cattle, for instance, the International Committee for Animal Recording provides a recording guideline for 1000 diagnoses that can be used toward the genetic improvement of health traits (ICAR GUIDELINES. Available online: https://www.icar.org/index.php/icar-recording-guidelines/, access on 20 February 2021). International corporations could work together in a joint effort for phenotyping or genotyping animals/disease to enlarge the resources and enhance the human capacity to deal with disease. For example, the use of automatic milking systems from different nations could improve the modeling of mastitis infections (Weigel & Shook, 2018) or the sharing of omics data could better develop the statistical methods and enhance understanding about the disease biology (Giuffra et al., 2019). The current 1000 Bull Genomes Project is a successful story regarding the sharing of genomic data for improving the prediction accuracy of future genomic EBVs (Hayes & Daetwyler, 2019). It is important to indicate that the increasing of the capacity of cloud storage and computing could also support the sharing of data and corporations.

2.4 CONCLUSIONS

Selecting favorable health traits to cope with diseases in farm animals has increasingly become an attractive focus of animal farming industries. Given some limitations and deficiencies of current non-selection disease control methods and the advantages of genetic selection over the other methods, breeding for health traits is a promising solution for the sustainable development of livestock farming. Although some remaining challenges regarding the accuracy of phenotyping and low heritability of disease traits hinder the progress of breeding for health traits, the advancement of sequencing techniques and affordable cost of genotyping make selective breeding more beneficial as a method for disease control but also require more storage and computing power. With the development of cloud computing, big data analyses increase the feasibility of selection for animal health traits. Increasing threats, such as climate change, have caused changes in the environments that require international collaborations to deal with the disease on a global scale. Eventually, smart farming with healthy animals and clean environments will be achieved with the sustainable selection methods of favorable health traits. The genetic and genomic selection solution, however, cannot address all the problems caused by disease farm animals. Therefore, it is necessary to accompany selection solution approaches with other disease control and monitor methods (e.g., vaccination, culling strategy, biosensor, and genome editing) to help animal agriculture industries to reduce the economic losses and animal welfare issues caused by farm animal diseases.

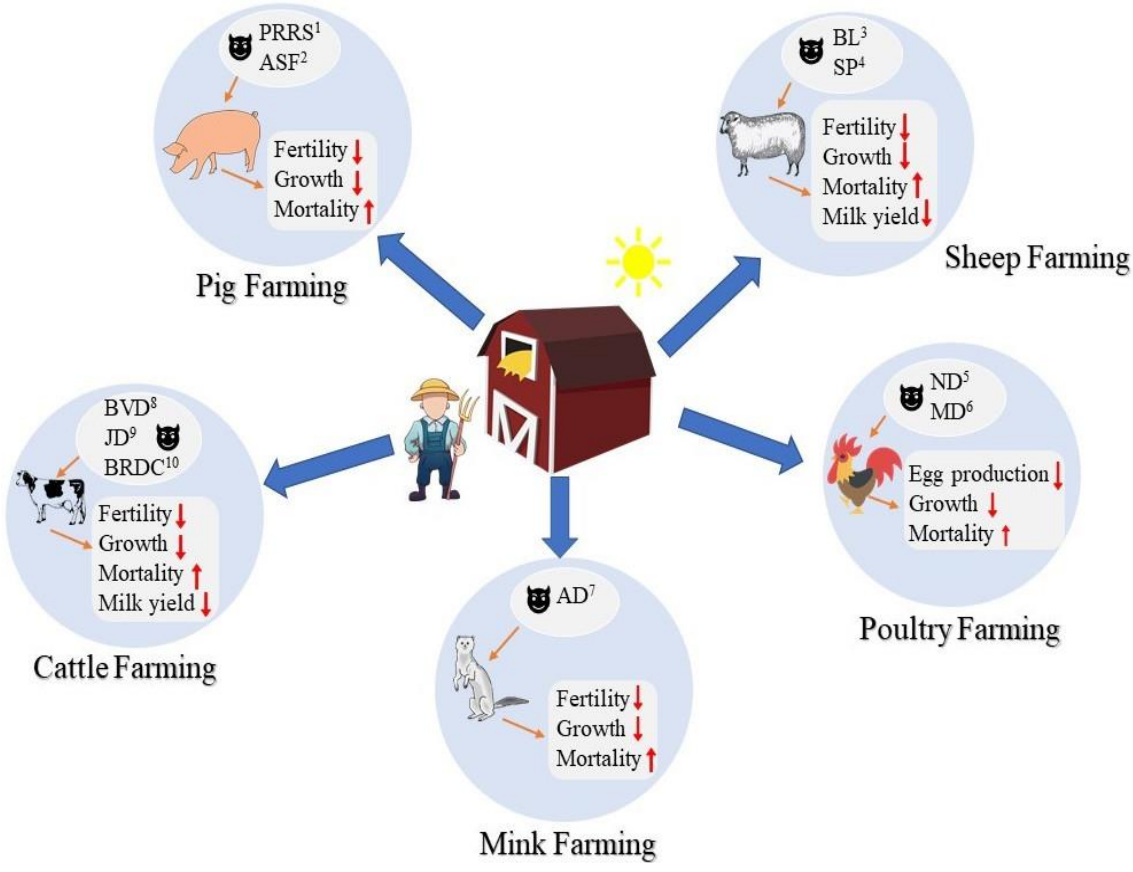

Figure 2.1 Economic consequences of common diseases in farm animals, including pig, sheep, poultry, mink, and cattle. The upward-pointing arrows refer to increase, and the downward-pointing arrows refer to decrease (PRRS1 = Porcine reproductive and respiratory syndrome; ASF2 = African swine fever; BL3 = Bluetongue; SP4 = Sheep pox; ND5 = Newcastle disease; MD6 = Marek's disease; AD7 = Aleutian disease; BVD8 = Bovine viral diarrhea; JD9 = Johne's disease; BRDC10 = Bovine respiratory disease complex).

Table 2.1 Prevalence and economic losses of common diseases and their impacts on performance in farm animal species.

Species	Disease	Prevalence	Economic Losses	Milk Yield	Fertility/Egg Production	Growth Rate	Mortality	Vaccine Available?	Specific Treatment?
Cattle	Bovine Viral Diarrhea	Up to 98.5% and 98.3% in non-vaccinated dairy and beef herds, respectively (Cowley et al., 2014)	40–100 thousand USD per herd in Canada (Carman et al., 1998) and 10–40 million USD per million calvings in Europe (Houe, 2003)	Reduced (~0.074 kg/day (Heuer et al., 2007))	Reduced (21% abortion rate (Roeder et al., 1986))	Reduced	High (~50% in calves (Khodakaram-Tafti & Farjanikish, 2017))	Yes	No
	Johne's Disease	68.1% of US dairy operations were infected (Attalla et al., 2010)	15 million CAD annually in Canada and 200–250 million USD in US (Cho et al., 2013)	Reduced (up to 25% (Losinger, 2005))	Reduced (7% lower rate of conception (VanLeeuwen et al., 2010))	Reduced	Culling infected individuals	Yes	No
	Bovine Respiratory Disease Complex	45.9% in UK dairy heifers(Johnson et al., 2017)	One billion USD annually in US (Neibergs et al., 2014)	N/A	N/A	Reduced	Moderate (~20% in calves (Urban-Chmiel et al., 2015))	Yes	No
Sheep	Bluetongue	19% in Italy (Carvelli et al., 2019) and up to 94.3% in Sudan (Elhassan et al., 2014)	In 2007, 12.6 million euros in the Netherlands (Velthuis et al., 2010)	Reduced (up to 42% (Barnard et al., 1998))	Reduced (25% abortion rate and 50% decrease in fertility (Toussaint et al., 2007))	Reduced	High (up to 41.5% (Conraths et al., 2009))	Yes	No
	Sheeppox	Up to 22% (Hota et al., 2018) in India and 40% in Ethiopia (Hurisa et al., 2018)	2.4 million USD annually in Maharashtra, India (Garner et al., 2000)	N/A	N/A	Reduced	High (up to 40% (Limon et al., 2020))	Yes	No

Table 2.1. Continued.

Species	Disease	Prevalence	Economic Losses	Milk Yield	Fertility/Egg Production	Growth Rate	Mortality	Vaccine Available?	Specific Treatment?
Swine	Porcine Reproductive and Respiratory Syndrome	Up to 48% of pig farms in Ontario, Canada (Arruda et al., 2015)	664 million USD annually in US (Holtkamp et al., 2013) and 130 million CAD annually in Canada (Mussell et al., 2011)	N/A	Reduced (up to 40% abortion rate (Pena et al., 2019))	Reduced	High (up to 100% (Pils et al., 2016))	Yes	No
	African Swine Fever	12.5% in China from August 2018 to July 2019 (Liu et al., 2019)	1.25 billion USD from 2007 to 2017 in Russia (USDA, 2017)	N/A	Reduced (54% abortion rate (Schlafer & Mebus, 1984))	N/A	High (30–70% (Sánchez-Cordón et al., 2018))	No	No
Poultry	Newcastle Disease	85.2% in eastern North America between 2009 and 2011 (Cross et al., 2013)	200 million USD from 2002 to 2003 in California, US (Wise et al., 2004)	N/A	Reduced (55% of egg production (Van Eck et al., 1976))	Reduced	High (up to 100% (Sedeik et al., 2019))	Yes	No
	Marek's Disease	49.5% in Iraq (Wajid et al., 2013)	1–2 billion USD annually worldwide (Dunn & Gimeno, 2013)	N/A	Reduced (decrease 5% egg production (Purchase, 1985))	Reduced	Moderate (10%–30% (Biggs & Nair, 2012))	Yes	No
Mink	Aleutian Disease	Up to 71% in Nova Scotia, Canada between 1998 and 2005 (Farid et al., 2012)	10 million USD in Denmark during 1984 (Farid et al., 2012)	N/A	Reduced fertility (~2.5 kits per whelping (Reichert & Kostro, 2014))	Reduced	High (30–100%(Henson et al., 1962))	No	No

Table 2.2 Strengths and weaknesses of common non-selection disease control methods in farm animals.

Controlling Method	Advantages	Disadvantages
Vaccination	▪ Prevent and mitigate various diseases in livestock ▪ Provide solutions to control diseases which have complex, limited or no treatment options available ▪ Decrease the antimicrobial resistance	▪ Only administered to healthy subjects ▪ May cause adverse reactions ▪ Bring expensive cost for large-scale use
Medical treatment	▪ Treat many common diseases in livestock species ▪ Increase in feed efficiency and performance	▪ Increase the occurrence of drug residues ▪ Increase the risk of drug resistance
Culling	▪ Main method used to control highly contagious and inextirpable diseases	▪ Fail in permanently eradicating some diseases from livestock farms ▪ High reinfection rate in some cases ▪ Very costly in large-scale farms
Genome editing	▪ Offer solutions to control untreatable diseases at affordable costs ▪ Has high efficiency and low cost in controlling diseases	▪ No legal regulations have been established to supervise genome-editing animals ▪ Is not mature enough for large-scale use ▪ Public's concerns
Biosensor	▪ Effective in disease detection and isolation, and health monitoring	▪ Not effective in practical livestock health management ▪ Not widespread and promoted due to the lack of investment
Probiotics	▪ Have great potential to reduce the risk of intestinal diseases ▪ Have the potential to replace some antibiotics	▪ Lacking adequate related research ▪ Unable to apply in large-scale livestock farming

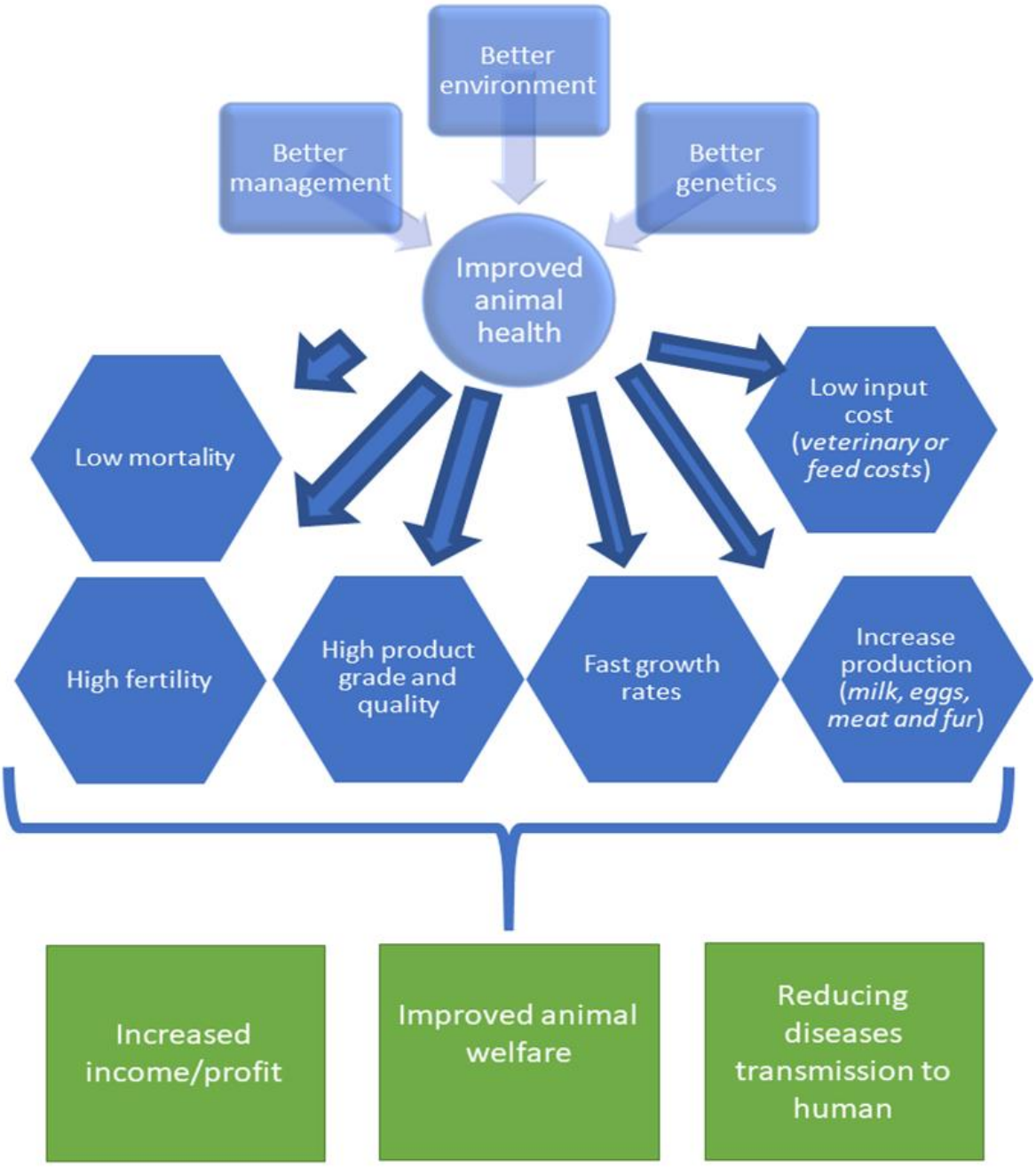

Figure 2.2 Overall benefits of selection for improved animal health.

Table 2.3 The number of quantitative trait loci (QTLs) detected in animal species by February 21, 2021.

Species	Number of Publications	Number of Traits	Overall	Health	Disease Suppressibility	Immune Capacity	Pathogens and Parasites	Blood Parameters
Cattle	1001	646	142,261	6380	2771	232	124	355
Chicken	328	430	12,246	820	739	NA	NA	294
Horse	94	56	2446	1128	1026	19	NA	1
Swine	698	691	30,580	6598	586	3230	81	2747
Sheep	173	262	3305	619	135	39	335	37

CHAPTER 3 : GENETIC AND PHENOTYPIC PARAMETERS FOR ALEUTIAN DISEASE TESTS AND THEIR CORRELATIONS WITH PELT QUALITY, REPRODUCTIVE PERFORMANCE, PACKED-CELL VOLUME, AND HARVEST LENGTH IN MINK[2]

3.1 INTRODUCTION

American mink (*Neovison vison*) is the primary source of fur for the fur industries worldwide, however, the severe economic losses caused by Aleutian diseases (**AD**) and other diseases such as the new coronavirus disease caused by severe acute respiratory coronavirus 2, the agent of the ongoing COVID-19 pandemic, make it difficult for mink farmers to maintain their business. Aleutian disease is induced by Aleutian mink disease virus (**AMDV**) infection and has been defined as an immune complex disease because the anti-AMDV antibodies produced by the immune system are not able to neutralize the virus but rather form infectious virus-antibody complexes (Stolze & Kaaden, 1987). The deposits of these infectious complexes could lead to lesions in the glomerulus and arteries (Porter et al., 1969; Cho & Ingram, 1973; Porter et al., 1973). The major clinical signs of AD-infected mink are hypergammaglobulinemia, glomerulonephritis, plasmacytosis, and arteritis (Eklund et al., 1968; Ingram & Cho, 1974). Aleutian disease is the most important disease of mink production worldwide, as it can cause serious anemia (McGuire et al., 1979), high adult and embryonic mortalities (Henson et al., 1962), low female reproductive performance (Henson et al., 1962; Reichert & Kostro, 2014), decreased body size (Kowalczyk et al., 2019), and low pelt quality (Farid & Ferns, 2011). These severe adverse

[2] A version of this chapter will be submitted to the Journal of Animal Science.

influences caused by AD result in tremendous financial losses to the mink farmers, and therefore, finding the practical solutions to control AD has become a top priority for the fur industry.

The test-and-remove strategy, culling mink with positive results of AD tests, has been applied as the primary method to control AD because of the ineffective immunoprophylaxis and medical treatment (Farid et al., 2018). Iodine agglutination test (**IAT**) and counterimmunoelectrophoresis (**CIEP**) are commonly employed in test-and-remove strategy. The IAT is a non-AD-specific test used to diagnose AD by detecting unhealthy animals with high amounts of serum gamma globulin, as AD is characterized in mink by marked hypergammaglobulinemia (Henson et al., 1962; Williams et al., 1965). This test has been used as a simple field procedure to detect mink infected with AMDV by several ranches in North America and Europe (Farid et al., 2018). However, a previous study reported that mink farms that attempted to eradicate AMDV by using IAT, ended with failure, and the owners gave up farming mink (Gunnarsson, 2001). The CIEP is an AD-specific test that can diagnose AD infected mink by detecting anti-AMDV antibodies in the blood (Farid et al., 2015). The CIEP test has been used for viral eradication in Nova Scotia province of Canada since the mid-1970s, but the AMDV infection is still a significant problem for the mink industry in this region (Farid et al., 2012). Iceland is the only country that successfully eradicated the AMDV in farmed mink for 12 years using CIEP between 1984 and 1996, but the virus was re-introduced during the late 1990s (Gunnarsson, 2001). Although Denmark has implemented a vigorous viral eradication program since the mid-1970s, the AMDV virus has still not been eradicated in Denmark (Christensen et al., 2011; Themudo et al., 2011). Several potential reasons, which include the variability of the virus

genome, the ineffectiveness of biosecurity, the infected wild animals in nature, and the persistent virus on the farms, lead to the inability of test-and-remove strategies (Farid et al., 2012; Canuti et al., 2016; Kashtanov & Salnikova, 2018).

The unsatisfactory outcome of the test-and-remove strategy has urged the fur industry in North America and Europe to select mink with low gamma globulin level or anti-AMDV antibody level, as hypergammaglobulinemia is one of the remarkable symptoms of AD (Henson et al., 1962; Williams et al., 1965) and the high level of anti-AMDV antibody can form the infectious virus-antibody complexes and enhance the AMDV infection (Porter et al., 1972; Kanno et al., 1993; Bloom et al., 1994; Aasted et al., 1998; Bloom et al., 2001). In Nova Scotia, a few farmers selected mink with resilience to the AMDV through assessing animal health and production, combining with IAT results (Farid & Ferns, 2017). Some AD positive mink farms in North America and Europe are selecting AD resilient mink with low anti-AMDV antibody level based on enzyme-linked immunosorbent assay (**ELISA**) test results, which is an AD-specific test used to identify and quantify the AMDV antibodies from mink sera samples (Knuuttila et al., 2009; Farid & Rupasinghe, 2016; Farid et al., 2018). The AMDV-G ELISA (**ELISA-G**) and VP2 ELISA (**ELISA-P**) systems are two main ELISA systems commonly employed in the mink industry. The ELISA-P system is an antigen-based ELISA based on VP2, which is a structural protein of AMDV (Knuuttila et al., 2009), and commonly used in the Netherlands and Finland (Farid & Rupasinghe, 2016). The ELISA-G system is an antigen-based ELISA based on AMDV-G, which is an *in vitro* cultured antigen (Aasted & Cohn, 1982), and commonly used in Denmark and North America (Farid & Rupasinghe, 2016).

Although some mink farmers have tried to apply AD-specific tests (ELISA and CIEP) or non-AD-specific test (IAT) in their breeding programs to select AD resilient mink, the feasibility of this procedure has not been verified. Meanwhile, estimation of genetic and phenotypic parameters are essential for designing an effective genetic evaluation program for traits of interest (Safari et al., 2005). However, to the best of our knowledge, the genetic analysis of AD tests and their correlations with pelt quality, female reproductive performance, packed-cell volume (PCV, an indication of the extent of anemia), and harvest length in mink has not been explored. This thesis chapter, therefore, aimed 1) to estimate the heritabilities for four AD tests (ELISA-G, ELISA-P, CIEP, and IAT), 2) to estimate the genetic and phenotypic correlations among AD tests, and 3) to estimate the genetic and phenotypic correlations between AD tests and two pelt quality traits, five female reproductive performance traits, PCV, and harvest length trait in mink.

3.2 MATERIALS AND METHODS

The proposed work was approved by the Dalhousie University Animal Care and Use Committee (certification#: 2018-009). All the mink used in this study were cared for based on the Code of Practice for the Care and Handling of Farmed Mink guidelines from Canada Mink Breeders Association (https:/www.nfacc.ca/pdfs/codes/mink_code_of_practice.pdf).

3.2.1 ANIMALS AND MANAGEMENT

Animals used in this research were raised under standard farming conditions at the Canadian Centre for Fur Animal Research (**CCFAR**) at Dalhousie University, Faculty of Agriculture (Truro, Nova Scotia, Canada) from 2006 to 2020. The studied mink were fed

with the same diets at the same production period, and the diets were adjusted according to the animal requirements in each production period. All mink had *ad libitum* access to the diet and water. The CCFAR was infected by AMDV in 2013; however, the origin of the virus has not been detected. The AMDV-contaminated feed and undetected contact with wild animals carrying AMDV were considered as the most likely causes. A persistent breeding program was not applied in CCFAR during these years (2006 to 2020), but animals that were weak and infertile were culled from the herd, and the individuals with satisfactory pelt quality and/or reproductive performances were selected for breeding. The total of 5,824 mink used in this study were the progeny of 1,051 sires and 2,097 dams. Pedigree information of 16 generations comprising 23,486 individuals was used.

3.2.2 ALEUTIAN DISEASE TESTS

Both AD-specific tests, including **ELISA-G**, **ELISA-P**, and **CIEP**, and non-AD-specific test of **IAT**, were employed in this research. Blood samples of the studied individuals were collected using the toenail clipping approach in mid-November of 2013 2014, 2018, and 2019 before selecting breeders. Blood samples of the selected breeders were collected again in mid-February of 2013 2014, 2017, 2018, 2019, and 2020 before mating. The blood sample combs (Figure A2.1) for ELISA test were shipped to Middleton Veterinary Services (**MVS**, Middleton, Canada) to conduct AMDV-G based ELISA and shipped to Nederlandse Federatie van Edelpelsdierenhouders (**NFE**, Wijchen, Netherlands) to conduct VP2 based ELISA (only samples from November 2018 and November 2019). Both ELISA-G and ELISA-P tests were applied to measure the amount of antibody against AMDV as optical density (**OD**). The levels of categories and the ranges of OD in each category were different

between MVS and NFE. In the MVS laboratory, the OD results obtained from ELISA-G tests were categorized into eight categories from 0 (low) to 7 (high), but in the NFE laboratory, the OD results obtained from ELISA-P tests were categorized into nine categories from 0 (low) to 8 (high). The CIEP tests were conducted at the Animal Health Laboratory at the University of Guelph (Guelph, Canada) to determine the existence of AMDV-specific antibodies, and the results were recorded as 0 (negative) and 1 (positive). The IAT tests were completed at CCFAR to measure the level of serum gamma globulin. The IAT results (Figure A3.1) were scored into four categories from 0 (clear) to 4 (dark clumpy precipitates).

3.2.3 PELT QUALITY EVALUATIONS

Live grading of pelt quality was performed in November 2018 and 2019 for mink in their first year. One skilled technician from North American Fur Auctions (**NAFA**) graded the pelt quality associated traits for all mink based on the NAFA live animal grading procedure. The traits included the overall pelt quality (**QUA**) and the pelt nap length (**NAP**). The QUA was an overall general impression of the fur, and the NAP was the length of the guard hair protruding from the underwool. The QUA was scored into three categories from 1 (poor) to 3 (best), and the NAP was scored into five categories from 1 (short) to 5 (long).

3.2.4 FEMALE REPRODUCTIVE PERFORMANCE MEASUREMENTS

Reproductive performances were recorded on paper forms (Figure A6.3) in each annual reproduction cycle from 2006 to 2020. The annual reproduction cycle in CCFAR included four periods. Mating was the first period where each female was moved into a male pen to

mate at the beginning of March. Whelping was the second period that lasted from late April to the middle of May. The interval between last mating and whelping or gestation length (**GL**), the total number of kits born (**KTB**, Figure A6.1), the number of newborn kits that survived 24-hr after birth (**KLB**, Figure A6.2), and the number of kits still alive at three weeks of age (**KL3**) were recorded during this period. Weaning was the third period where the kits were separated from their dams and moved into new cages at the end of June when they were approximately 6-8 weeks old. The number of kits still alive at weaning age (**KLW**) was recorded during this period. Selection was the fourth period where mink were selected for pelting or breeding depending on their phenotypes (e.g. fur grades, disease history, and weight) in late November or early December.

3.2.5 PACKED-CELL VOLUME TEST

Packed-cell volume (**PCV**), which is employed to measure the volume percentage of red blood cells in the blood and widely used as an indication of the extent of anemia, was performed as an additional health test in CCFAR, as AD infected mink could develop severe anemia within a few months after infection (McGuire et al., 1979). Blood tests were conducted in the CCFAR laboratory. Blood samples were centrifuged first, and the PCV results were read using hematocrit reader (Figure A4.1). The normal range of PCV for healthy male and female mink is from 46.5% to 61.0% and from 35.0% to 56.5%, respectively (Fletch & Karstad, 1972).

3.2.6 HARVEST LENGTH MEASUREMENT

The body length of mink at harvest (**HL**) was measured by using measurement board (Figure A5.1) at two different harvest times. The HL were measured on the harvest days in December 2018 and 2019 for mink that were not selected as breeders for the following breeding seasons. Additionally, HL were measured on the harvest days in February 2019 and 2020 for sires that completed their breeding tasks and dams that were mated but failed to be pregnant.

3.2.7 STATISTICAL ANALYSES

The data quality control was performed using CFC and R software. The accuracy of the pedigree file was checked by CFC software (Sargolzaei et al., 2006). The R software was used to draw and check the distribution of raw data. The outliers were detected by checking if the data record was more or less than three standard deviations from the mean. All detected outliers were double-checked with the technicians and phenotypic records documents in CCFAR before removing them.

A univariate animal model was primarily applied to estimate the variance components of random additive genetic, permanent environmental, and maternal effects. The model is given by

$$\boldsymbol{y} = \boldsymbol{Xb} + \boldsymbol{Za} + \boldsymbol{Wpe} + \boldsymbol{Gm} + \boldsymbol{e},$$

where $\boldsymbol{y}$ is the vector of phenotypic observations; $\boldsymbol{b}$ is the vector of fixed effects; $\boldsymbol{a}$ is the vector of random additive genetic effects; $\boldsymbol{pe}$ is the vector of random permanent environmental effects; $\boldsymbol{m}$ is the vector of random maternal effects; and **e** is the vector of

residual effects; and $\boldsymbol{X}$, $\boldsymbol{Z}$, $\boldsymbol{W}$, and $\boldsymbol{G}$ are the incidence matrices relating the phenotypic observations to fixed, random additive genetic, permanent environmental, and maternal effects, respectively. It was assumed that random effects are independent and normally distributed:

$$a \sim N(0, \boldsymbol{A}\sigma_a^2), pe \sim N\left(0, \boldsymbol{I}\sigma_{pe}^2\right), m \sim N(0, \boldsymbol{A}\sigma_m^2), and\ e \sim N(0, \boldsymbol{I}\sigma_e^2),$$

where $\boldsymbol{A}$ is the numerator relationship matrix; $\boldsymbol{I}$ is an identity matrix; $\boldsymbol{\sigma_a^2}$, $\boldsymbol{\sigma_{pe}^2}$, $\boldsymbol{\sigma_m^2}$, and $\boldsymbol{\sigma_e^2}$ are the variances of random additive genetic, permanent environmental, maternal, and residual effects. Fixed effects were sex (male and female), year (2006 to 2020), and color type (brown, breath of spring, dark, demi, gray, mahogany, pastel, sapphire, stardust, white, and white-blue). In other livestock species, it is usual to include a fixed effect of the breed. However, in mink, the definitive breeds in mink are missing, and mink are categorized by color-types in current mink farming and market. In addition, the previous study has shown that the color-types affected the performance traits in mink (Liu et al., 2011). Meanwhile, disease signs with AMDV vary with the coat color of mink (Jensen et al, 2011), and mink with blue-grey coat color are more susceptible and severely affected than other colors (Hadlow et al., 1983, Bloom et al., 1994). In addition, the genetic structure analysis using genomic data in the same population (CCFAR population) showed that the molecular variance among color-types was significant ($P<0.001$) and accounted for 18% of the total variation (Karimi et al., 2021b). Therefore, the effect of color-types in the current traits were tested. Meanwhile, numbers of mating (1 to 3 times) and dam age (1 to 5 years) were also used as fixed effects for GL, KTB, KLB, KL3, and KLW. The age of mink at test day (in days) was used as a covariate for ELISA-G, ELISA-P, CIEP, IAT, and PCV, and harvest age (in days) was used as a covariate for HL.

The significances of fixed effects, covariates, and random effects were determined using ASReml 4.1 software (Gilmour et al., 2018). The significance of fixed effects and covariates were statistically tested using the REML procedure in ASReml 4.1 software (Gilmour et al., 2018), and only significant (P<0.05) effects were kept in the mixed model analyses for each trait (Table 3.1). The significance of different random effects for each trait was determined by comparing the full model and the reduced model using the following statistic:

$$-2\left(logL_{reduced\ model} - logL_{full\ model}\right)$$

$$\sim\chi^2_{df\ (full\ model)-\ df\ (reduced\ model),}$$

where log*L* was the log likelihood values for the different models; and df was the degrees of freedom in each model (df=1), respectively. Random permanent environmental effect was only significant (P<0.05) for ELISA-G. Random maternal effect was significant (P<0.05) for ELISA-P, CIEP, and GL.

Bivariate models were used to estimate the genetic and phenotypic correlations between traits using ASReml 4.1 software (Gilmour et al., 2018). Relevant significant (P<0.05) fixed and random effects were included in bivariate analyses for each trait (Table 3.1). Generally, the following bivariate model was used to analyze the traits:

$$\begin{bmatrix}\boldsymbol{y_1}\\ \boldsymbol{y_2}\end{bmatrix} = \begin{bmatrix}\boldsymbol{X_1} & 0\\ 0 & \boldsymbol{X_2}\end{bmatrix}\begin{bmatrix}\boldsymbol{b_1}\\ \boldsymbol{b_2}\end{bmatrix} + \begin{bmatrix}\boldsymbol{Z_{a1}} & 0\\ 0 & \boldsymbol{Z_{a2}}\end{bmatrix}\begin{bmatrix}\boldsymbol{a_1}\\ \boldsymbol{a_2}\end{bmatrix} + \begin{bmatrix}\boldsymbol{Z_{pe1}} & 0\\ 0 & \boldsymbol{Z_{pe2}}\end{bmatrix}\begin{bmatrix}\boldsymbol{pe_1}\\ \boldsymbol{pe_2}\end{bmatrix} + \begin{bmatrix}\boldsymbol{Z_{m1}} & 0\\ 0 & \boldsymbol{Z_{m2}}\end{bmatrix}\begin{bmatrix}\boldsymbol{m_1}\\ \boldsymbol{m_2}\end{bmatrix} + \begin{bmatrix}\boldsymbol{e_1}\\ \boldsymbol{e_2}\end{bmatrix},$$

where $\boldsymbol{y_1}$ and $\boldsymbol{y_2}$ are the vectors of observations for the first and second traits; $\boldsymbol{b_1}$, $\boldsymbol{b_2}$, $\boldsymbol{a_1}$, $\boldsymbol{a_2}$, $\boldsymbol{pe_1}$, $\boldsymbol{pe_2}$, $\boldsymbol{m_1}$, $\boldsymbol{m_2}$, $\boldsymbol{e_1}$, and $\boldsymbol{e_2}$ are the vectors of fixed, random additive genetic, permanent environmental, maternal, and residual effects for traits 1 and 2, respectively; and $\boldsymbol{X_1}$, $\boldsymbol{X_2}$,

$\boldsymbol{Z_{a1}}$, $\boldsymbol{Z_{a2}}$, $\boldsymbol{Z_{pe1}}$, $\boldsymbol{Z_{pe2}}$, $\boldsymbol{Z_{m1}}$, and $\boldsymbol{Z_{m2}}$, are the incidence matrices relating observations to fixed, random additive genetic, permanent environmental, and maternal effects for traits 1 and 2, respectively. Random additive genetic effects were included in the final model for all traits, but the permanent environmental effect was only included for ELISA-G, and the random maternal effect was only included for ELISA-G, ELISA-P, CIEP, and GL. It was assumed that the random effects were normally distributed:

$$\begin{bmatrix} \boldsymbol{a_1} \\ \boldsymbol{a_2} \end{bmatrix} \sim N\left(0, \boldsymbol{A} \otimes \begin{bmatrix} \boldsymbol{\sigma^2_{a1}} & \boldsymbol{\sigma_{a1a2}} \\ \boldsymbol{\sigma_{a1a2}} & \boldsymbol{\sigma^2_{a2}} \end{bmatrix}\right),$$

$$\begin{bmatrix} \boldsymbol{pe_1} \\ \boldsymbol{pe_2} \end{bmatrix} \sim N\left(0, \boldsymbol{I} \otimes \begin{bmatrix} \boldsymbol{\sigma^2_{pe1}} & \boldsymbol{\sigma_{pe1pe2}} \\ \boldsymbol{\sigma_{pe1pe2}} & \boldsymbol{\sigma^2_{pe2}} \end{bmatrix}\right),$$

$$\begin{bmatrix} \boldsymbol{m_1} \\ \boldsymbol{m_2} \end{bmatrix} \sim N\left(0, \boldsymbol{A} \otimes \begin{bmatrix} \boldsymbol{\sigma^2_{m1}} & \boldsymbol{\sigma_{m1m2}} \\ \boldsymbol{\sigma_{m1m2}} & \boldsymbol{\sigma^2_{m2}} \end{bmatrix}\right), \text{ and}$$

$$\begin{bmatrix} \boldsymbol{e_1} \\ \boldsymbol{e_2} \end{bmatrix} \sim N\left(0, \boldsymbol{I} \otimes \begin{bmatrix} \boldsymbol{\sigma^2_{e1}} & \boldsymbol{\sigma_{e1e2}} \\ \boldsymbol{\sigma_{e1e2}} & \boldsymbol{\sigma^2_{e2}} \end{bmatrix}\right),$$

where $\boldsymbol{A}$ is the numerator relationship matrix; $\boldsymbol{I}$ is an identity matrix; $\boldsymbol{\sigma^2_{a1}}$, $\boldsymbol{\sigma^2_{a2}}$, $\boldsymbol{\sigma^2_{pe1}}$, $\boldsymbol{\sigma^2_{pe2}}$, $\boldsymbol{\sigma^2_{m1}}$, and $\boldsymbol{\sigma^2_{m2}}$ are the variances of random additive genetic, permanent environmental, maternal, and residual effects for traits 1 and 2, respectively; $\boldsymbol{\sigma_{a1a2}}$, $\boldsymbol{\sigma_{pe1pe2}}$, $\boldsymbol{\sigma_{m1m2}}$, and $\boldsymbol{\sigma_{e1e2}}$ are the covariances of random additive genetic, permanent environmental, maternal, and residual effects between traits 1 and 2, respectively.

Phenotypic variances were calculated as $\sigma_p^2 = \sigma_a^2+\sigma_e^2$ for IAT, NAP, QUA, KTB, KLB, KL3, KLW, PCV, and HL, as $\sigma_p^2 = \sigma_a^2+ \sigma_m^2+\sigma_e^2$ for ELISA-P CIEP, and GL, and as $\sigma_p^2 = \sigma_a^2+\sigma_{pe}^2+\sigma_m^2+\sigma_e^2$ for ELISA-G. Heritability (h^2) was defined as follows:

$$h^2 = \frac{\sigma_a^2}{\sigma_p^2}.$$

The final reported heritability and its standard error for each trait in Table 3.4 were obtained by averaging the estimates of multiple corresponding pairwise bivariate analyses. Repeatability (r^2) was defined as follows:

$$r^2 = \frac{\sigma_a^2 + \sigma_{pe}^2}{\sigma_p^2}.$$

Phenotypic and genetic correlations among traits were calculated based on the (co)variance components from bivariate models.

3.3 RESULTS AND DISCUSSION

3.3.1 DESCRIPTIVE STATISTICS

The number of records, mean, standard deviation (**SD**), range, and coefficient of variation (**CV**) for each trait are presented in Table 3.2. The numbers of data records varied among the analyzed traits. Female reproductive performance traits had more records than the other studied traits because CCFAR started recoding these traits in 2006 and began recording other traits after 2015. The ELISA-G had more records (1,207 records more) than ELISA-P in CCFAR farm since ELISA-G has been applied longer in North America than ELISA-P, which is commonly used in the Netherlands and Finland. The NAP, QUA, and HL had less than 1,000 records (844 to 960) because these traits were new traits in CCFAR and were only recorded after 2017.

The highest three CVs were 163.16% for IAT, 112.67% for ELISA-G, and 100.93% for ELISA-P. These results implied that there is a great potential to select mink with low

ELISA and IAT scores. Compared with other traits, the lowest two CVs were observed on PCV (7.82%) and HL (9.94%). The CVs previously reported for body length of mink at harvest were in the range of 5.53% to 9.20% (Zongyue et al., 2016; Thirstrup et al., 2017), which were almost the same as the CV of harvest body length obtained in this study. The CVs of litter size traits were ranged from 40.61 to 55.26%, which were similar to the range (36 to 53%) reported by the previous studies (Hansen et al., 2010; Koivula et al., 2010). Similar to Karimi et al. (2018), we also reported that the average number of kits decreased from 6.60 per dam at birth to 5.70 per dam at 24-hr after whelping and further decreased to 4.21 per dam at weaning.

3.3.2 RANDOM MATERNAL AND PERMANENT ENVIRONMENTAL EFFECTS

The estimated variance components, heritability, the proportion of random permanent environmental and maternal effects, and repeatability for each trait are presented in Table 3.3. Random maternal effect was significant ($P<0.05$) for ELISA-G, ELISA-P, CIEP, and GL (Table 3.1) and explained 10%, 8%, 14%, and 5% of their phenotypic variances, respectively (Table 3.3). To the best of our knowledge, no previous study about the significance of random maternal effects on AD-specific tests (ELISA and CIEP) was available for comparison. However, in dairy cattle, the random maternal effects could explain 1 to 3% of the phenotypic variances of milk ELISA scores for Johne's disease (Mortensen et al., 2004; Attalla et al., 2010), which was lower than our estimations (8% for ELISA-G to 10% for ELISA-P). In Holstein cattle, the random maternal effect explained 25.7% of the phenotypic variances of sera ELISA for *Neospora caninum* (Pan et al., 2004), which was higher than the present result. The different statistical models, samples (sera or

milk) for ELISA test, transformations of ELISA test results (categorical or continuous), and types of diseases (virus or bacterium) might cause these discrepancies.

Random permanent environmental effect was only significant ($P<0.05$) for ELISA-G and explained 23% of its phenotypic variance (Tables 3.1 and 3.3). Although there is no relevant literature for AD in mink, but in dairy cattle, the random permanent environmental effect explained 25% of the phenotypic variances of milk ELISA scores for Johne's disease (Pritchard et al., 2017b), which was similar to the results of the current study. Repeatability (±SE) of ELISA-G was estimated at 0.58±0.04 (Table 3.3). The high repeatability of ELISA-G implied that repeated measures on the same mink have substantially less variation than measures of different individuals. In other words, the previous records of ELISA-G are good indicators for the future records of ELISA-G tests. The repeatability, meanwhile, is a measure to predict probable response to selection in the current generation. The high repeatability of ELISA-G also indicated that the test scores of ELISA-G in the current generation could be reduced by genetic selection of individuals with low ELISA-G scores in the current population. Except for selected breeders, most of the farmed commercial mink will be only kept on the farm for less than nine months. Therefore, mink farmers could use a single ELISA-G test in their selection decisions instead of repeating the tests on the same individual because mink with low ELISA-G score tend to remain low in the following ELISA-G tests.

3.3.3 HERITABILITY ESTIMATES

Heritability estimates (±SE) for AD tests are presented in Table 3.4 (diagonal elements). Estimated heritability (±SE) was 0.39±0.06 for ELISA-G and 0.61±0.07 for ELISA-P. The

estimated moderate-to-high heritabilities of ELISA tests for AD indicated that the selection of mink with low anti-AMDV antibody titer is feasible through traditional genetic selection. To the best of our knowledge, the heritability of ELISA test results for AD has not been reported in the previous studies, and therefore, no previous estimates are available for comparison. However, the heritabilities of ELISA test results for other diseases were estimated in other species. For example, the heritabilities of the ELISA tests for Johne's disease in dairy cattle were estimated at the range of 0.07 to 0.16 (Gonda et al., 2006; Attalla et al., 2010), which are less than our estimates. In chicken populations, the heritability of ELISA tests for Newcastle disease was estimated at 0.48 (Liu et al., 2014), which is in the range of our estimates (0.39-0.61). In pigs, the heritability of serum ELISA test for the porcine reproductive and respiratory syndrome (PRRS) was estimated at 0.45 (Serão et al., 2014), which is also in the range of our estimates (0.39-0.61). Several factors could lead to the variation in the heritability estimations for ELISA among these studies. Different approaches used to process the raw data is one of the potential reasons causing these inconsistencies. For instance, ELISA test results were analyzed both as a binary trait (positive or negative) and as a linear trait as the transformed ELISA optical density in the Attalla et al. (2010) study, but the ELISA results were expressed as a sample-to-positive ratio in the Liu et al. (2014) study for antibody response of chickens to Newcastle disease and Avian Influenza and the Serão et al. (2014) study for antibody response of pigs to PRRS. The sample size is another reason that leads to the differences among estimations. In this study, the sample size (2,359 ELISA-G records from 1,874 individuals and 1,152 ELISA-P records from 1,115 individuals) was smaller than the sample size in Attalla et al. (2010) study (43,841 ELISA tests from 36,209 cows) and Serão et al. (2014) estimation (ELISA on 5,227 litters from 1,967 sows) but larger than Liu et al. (2014) study (511 ELISA records

from 511 birds). Additionally, other factors, including statistical models, breeding structure, pedigree completeness, and disease differences between species were also contributed to these discrepancies.

The estimated heritability for ELISA-G (0.39±0.06) was lower than that of ELISA-P (0.61±0.07); however, a very strong positive genetic correlation (0.99±0.01) between these two traits indicated that these two different ELISA systems measured the same trait (Table 3.4). The availability of more records on ELISA-G with repeated measurements in different generations and the different number of categories for each trait are the potential reasons that lead to the non-significancy ($P>0.05$) of year, sex, and permanent environmental effects for ELISA-P (Table 3.3). This could cause differences in the estimated heritabilities for these ELISA tests. As the number of records of ELISA-G was more than twice the number of records of ELISA-P (Table 3.2), more repeated measurements were observed on the ELISA-G records (234 individuals had at least two repeated measurements, and up to four repeated measurements on the same individual) than ELISA-P (only 37 individuals had two repeated measurements). Meanwhile, the ELISA-G records were collected over seven generations compared to four generations of ELISA-P. Although the heritabilities for these two ELISA tests were estimated to be different, their moderate-to-high heritabilities suggested that the phenotypic observation on ELISA-G and ELISA-P could be good indicators for mink farmers to select mink with low anti-AMDV level in order to reduce the AMDV infection caused by the high level of infectious virus-antibody complexes.

Our estimated heritability of CIEP was low (0.11±0.07), indicating the presence of small additive genetic effects on CIEP (Table 3.3). Only two studies estimated the heritability of CIEP test for AD that were moderate to high. The estimated heritabilities for CIEP-positive

mink kits at four and seven months of age were in the range of 0.22 to 0.58 (Farid et al., 2018; Farid, 2020), which were higher than our estimate of 0.11. The statistical models and sample size are the potential reasons leading to these discrepancies. The random maternal effect was significant ($P<0.05$) for CIEP test in our study. However, Farid et al. (2018) and Farid (2020), did not test the significance of random maternal effects and permanent environmental effects. Meanwhile, our sample size (1,127 CIEP records from 1,092 individuals in four generations) was larger than the sample size of Farid (2020) study (945 CIEP records from 534 individuals in two generations). The low heritability of CIEP indicated the ineffectiveness of direct selection for CIEP results based on their phenotypic observations. Therefore, the indirect selection and advance genomic selection will be more appropriate for the mink industry to select mink with the negative CIEP test result.

The estimated heritability (±SE) for IAT was 0.26±0.05 (Table 3.3). The moderate heritability of IAT indicated that the traditional genetic selection could be an appropriate method to reduce the level of gamma globulin in AD positive farms by selecting mink with lower IAT scores. To the best of our knowledge, this estimate is a new contribution to the mink research and warrants further investigation. The IAT was not applied for the diagnosis of other species diseases as it was only used as a non-AD-specific test to diagnose AD by detecting mink with hypergammaglobulinemia (Gorham, 1972). The estimated moderate heritability of IAT suggested that the mink farmers could use IAT as an indicator to select mink with low level of gamma globulin, and therefore reduce the adverse health problems caused by hypergammaglobulinemia in AD epidemic farms.

3.3.4 CORRELATIONS AMONG ALEUTIAN DISEASE TESTS

Phenotypic and genetic correlations among AD tests are presented in Table 3.4. All the phenotypic and genetic correlations among AD traits were significant ($P<0.05$) except for the genetic correlation between ELISA-G and CIEP (0.33±0.20). The ELISA-G had high phenotypic (0.83±0.01) and genetic (0.99±0.01) correlations with ELISA-P indicating that these ELISA systems were highly correlated, and they measured the same phenotype (anti-AMDV antibody level) in this mink population. The CIEP showed a slightly lower phenotypic correlation (0.26±0.03) with ELISA-G than ELISA-P (0.34±0.03). In another study, CIEP had higher phenotypic correlations with ELISA-G (0.43 to 0.63) and ELISA-P (0.81 to 0.83) than our estimates (Farid & Rupasinghe, 2016). The different formats of CIEP records, statistical methods, and sample size are the potential reasons causing these inconsistencies. Compared with our study, in which CIEP was treated as a binary trait (positive and negative), Farid and Rupasinghe (2016) used the CIEP records as the titre of anti-AMDV antibodies and transformed them to $\log_2(\text{CIEP}) = 0$ if CIEP = 0 and $\log_2(\text{CIEP}) + 1$ if CIEP > 0. In this study, bivariate animal models were used to estimate the phenotypic correlations between CIPE and ELISA tests, but in Farid and Rupasinghe (2016) study, the correlations between CIEP and the ELISA results were determined by Spearman's rank correlation. Meanwhile, only 880 mink were used in Farid and Rupasinghe (2016) study, but more than 1,127 mink were used in our study to estimate the genetic and phenotypic parameters of CIEP. The ELISA-P showed high positive genetic correlation (0.63±0.18) with CIEP, which indicated that selection for negative CIEP would reduce the score of ELISA-P test. On the other hand, ELISA-P could be used as an indicator for indirect selection of CIEP, as ELISA-P had higher heritability (0.61±0.07) than CIEP (0.11±0.07) with a significant ($P<0.05$) positive genetic correlation with CIEP. To our knowledge, there

was no information available about the genetic correlations among ELISA-G, ELISA-P, and CIEP in the literature and this warrants further investigation.

Both ELISA-G and ELISA-P had moderate positive phenotypic correlations with IAT (0.42±0.03 and 0.42±0.02, respectively). These significant ($P<0.05$) phenotypic correlations are expected since the infection with AMDV could cause progressive hypergammaglobulinemia (Williams et al., 1965); and therefore, higher IAT scores were observed on AMDV-infected mink, as IAT is used to measure the level of serum gamma globulin (Henson et al., 1962). Both ELISA-G and ELISA-P showed strong positive genetic correlations with IAT (0.83±0.07 and 0.73±0.08, respectively). These significant ($P<0.05$) strong positive genetic correlations indicated that IAT could be a good indicator for selecting mink with low anti-AMDV antibody level. Therefore, IAT can be applied as an economical and convenient test to help the AD epidemic mink ranches to indirectly select mink with low anti-AMDV antibody level. The IAT also showed a significant ($P<0.05$) moderate positive genetic correlation with CIEP (0.48±0.22), which indicated that the selection of lower IAT score could decrease the CIEP score. Therefore, mink farmers could also apply IAT as an indictor to indirectly select mink with negative CIEP results, as IAT was estimated to have higher heritability (0.26±0.05) than CIEP (0.11±0.07) and have significant ($P<0.05$) positive genetic correlation with CIEP. To our knowledge, the genetic correlations among AD tests were not investigated in the other studies, and it is worthy of further validation.

3.3.5 CORRELATIONS BETWEEN ALEUTIAN DISEASE TESTS AND PELT QUALITY TRAITS

Phenotypic and genetic correlations between AD tests and pelt quality traits are shown in Tables 3.5 and 3.6, respectively. Among all AD test traits, only IAT showed a significant ($P<0.05$) low negative phenotypic correlation (-0.09±0.04) and a significant ($P<0.05$) moderate negative genetic correlation (-0.39±0.12) with NAP (Table 3.5). These estimated results indicated that the selection of mink with lower IAT scores could increase the length of fur nap in mink pelt. The fur nap gives the mink pelt its shine and color. The nap length of pelt is important because the short-napped pelts are used in fashion, while the long-napped pelts are mostly seen in trim these days (Ward, 2016). Therefore, selecting mink with low IAT scores could lead to the undesired long nap pelt and affect the pelt price. No AD-specific tests (ELISA-G, ELISA-P, and CIEP) showed significant genetic correlations with QUA and NAP, which indicated that the selection of favorable AD-specific tests (lower ELISA test score or negative CIEP) would not cause adverse influences on the nap length of pelt and overall pelt quality. Therefore, mink farmers could select mink with low anti-AMDV antibody based on ELISA tests without the adverse impacts on the quality of pelt. Again, these estimates of genetic correlations between AD tests and pelt quality traits are new in the present study, and no estimates were available in the literature and warrant further investigation. However, the genetic correlation between disease traits and wool or fur related traits were studied in other species. For example, in sheep, the genetic correlations between fleece weight and fecal egg count, which was used to measure the *Nematodirus*, was estimated in the range of 0.11±0.02 to 0.17±0.02 (Pickering et al., 2012), which was lower than our estimates. In Finnish blue fox, the genetic correlation between eye infection and fur density was estimated at -0.49±0.20 (Kempe & Strandén, 2016),

which was higher than the estimated value in this study. Many potential factors including statistical models, breeding structure, pedigree completeness, sample size, trait definition, different pathologies and transmission between diseases, and purity of breeds, were considered as the causes leading to these inconsistencies.

3.3.6 CORRELATIONS BETWEEN ALEUTIAN DISEASE TESTS AND FEMALE REPRODUCTIVE PERFORMANCE TRAITS

Phenotypic and genetic correlations between AD tests and female reproductive performance traits are shown in Tables 3.5 and 3.6, respectively. Only ELISA-G had a significant ($P<0.05$) low negative phenotypic correlation with KLW (-0.14±0.05). Although this phenotypic correlation was low, but this was expected because the infection of dams with AMDV before pregnancy could decrease the number of weaned kits per dam (Reichert & Kostro, 2014). Both ELISA-G and ELISA-P showed moderate negative genetic correlations with and KLW (-0.49±0.12 and -0.48±0.24, respectively), which indicated that the selection of dams with lower anti-AMDV antibody levels could increase the number of kits alive at weaning age. Currently, mink farmers use the phenotypic information of pre-breeding ELISA score for selection of potential breeders. The findings in this thesis indicated that the genetic selection of female mink with lower pre-breeding ELISA scores could reduce the adverse influences caused by AD on litter size in AD positive mink farms, as the number of kits alive at weaning has been considered as an applicable criterion to improve the litter size in mink populations (Karimi et al., 2018). Therefore, the genetic selection of ELISA scores can help AD epidemic mink farms to reduce the adverse influences of AD on litter size. The ELISA-G also showed significant

(P<0.05) moderate negative but favorable genetic correlations with other litter size traits (-0.41±0.16 with KTB, -0.43±0.18 with KLB, and -0.43±0.13 with KL3). These results indicated that selecting dams with lower scores of ELISA-G could improve the total number of kits born and increase the number of newborn kits at 24-hr after birth, three weeks of age, and weaning age. Therefore, it is suggested that mink farmers could select their female breeders based on lower ELISA-G score to improve their reproductive performance. To our knowledge, no genetic correlation estimates are available between ELISA tests of AD and female reproductive performance traits in mink, and it would worth further investigation. In swine, however, Serão et al. (2014) found that the ELISA test results for PRRS disease showed strong positive genetic correlations with the number of piglets born alive (0.73) and the number of piglets live at 24-hr (0.73) and strong negative genetic correlations with the number of stillborn piglets (-0.72) and the percentage of piglets born dead (-0.70). These differences might be from the different pathogeneses of AD versus PRRS. Aleutian disease of mink is an immune complex disease induced by a viral infection. The AMDV cannot be neutralized in vivo by the presence of high concentrations of anti-AMDV antibody in serum (Aasted et al., 1984; Porter et al., 1984). In fact, high level of anti-AMDV antibody can enhance the AMDV infection (Porter et al., 1972; Kanno et al., 1993; Bloom et al., 1994; Aasted et al., 1998; Bloom et al., 2001). Therefore, the higher level of anti-AMDV antibody is harmful to the host. In swine, inversely, selection for higher immune antibody response to PRRS, which is an infectious viral disease characterized by reproductive failure in sows and respiratory distress in piglets and fattening pigs, has the potential to provide aid in PRRS containment (Lewis et al., 2007; Hess et al., 2016; Dekkers et al., 2017). In addition, several other factors, including

statistical models, sample size, the transformation of raw ELISA results, and purity of breeds, were also the potential reasons cause these inconsistencies.

Despite nonsignificant (P>0.05) genetic correlations between CIEP and female reproductive performance traits, the significant (P<0.05) phenotypic correlations were observed for CIEP with GL, KTB, and KLB (-0.37±0.09, 0.44±0.09, and 0.38±0.10, respectively) indicated that environmental effects play important roles in the interaction among these traits. The IAT did not show significant (P>0.05) genetic correlations with female reproductive performance traits. The nonsignificant (P>0.05) genetic correlations of CIEP and IAT with female reproductive performance indicated that the selection of CIEP or IAT would not influence the reproductive performance of dams in AD positive farming environments. In other words, mink farmers can simultaneously select female mink with negative CIEP results or low IAT and favorable reproductive performance traits without causing adverse influences on each other. To the best of our knowledge, this is the first report for these correlations.

3.3.7 CORRELATIONS BETWEEN ALEUTIAN DISEASE TESTS AND PACKED-CELL VOLUME

Both ELISA-G and ELISA-P had significant (P<0.05) moderate negative phenotypic correlation with PCV, which were -0.33±0.03 and -0.37±0.03, respectively (Table 3.5). The CIEP showed a significant (P<0.05) low negative phenotypic correlation with PCV (-0.10±0.03). These results were expected as the AMDV-infected mink could develop severe anemia after infection (McGuire et al., 1979), and therefore, lower PCV scores could be observed on AMDV-infected mink. The ELISA-G, ELISA-P, and IAT showed moderate

negative genetic correlations with PCV, which were -0.53±0.09, -0.40±0.10, and -0.56±0.10, respectively (Table 3.6). These results suggested that selecting mink with lower ELISA or IAT scores could increase the level of red blood cells in AD positive mink populations. To the best of our knowledge, the genetic correlations between AD tests and PCV were not investigated in the previous mink studies, however, the genetic correlations between other disease tests and PCV were estimated in other livestock species. For example, in dairy goats, the genetic correlation between fecal egg counts, which has been used as a test for gastrointestinal parasitism disease, and PCV was estimated to be -0.41 (Heckendorn et al., 2017), which was in agreement with our results. The estimated significant ($P<0.05$) genetic correlations between ELISA tests and PCV suggested that the mink farmers could select mink with low ELISA-G or ELISA-P score to reduce the risk of anemia caused by AD on farmed mink in AD positive farm. Meanwhile, mink farmers could apply PCV test as an indicator to indirectly select mink with low ELISA test scores, as it had a moderate heritability (0.34±0.05, Table 3.3) and significant ($P<0.05$) moderate negative genetic correlations with ELISA-G and ELISA-P.

3.3.8 CORRELATIONS BETWEEN ALEUTIAN DISEASE TESTS AND HARVEST LENGTH

Phenotypic and genetic correlations between AD tests and harvest length are shown in Tables 3.5 and 3.6, respectively. Only ELISA-G showed a significant ($P<0.05$) low phenotypic correlation with HL (-0.30±0.06). Except for ELISA-G, all other AD tests did not show significant ($P>0.05$) genetic correlations with HL, which indicated that selection on favorable ELISA-P, CIEP, and IAT results would not significantly change HL. The

ELISA-G was the only AD test that had a significant ($P<0.05$) moderate genetic correlation with HL (-0.45±0.16) indicating that the selection of mink with a lower ELISA-G score could increase the body length of mink at harvest. The body length is one of the most important production traits for mink farmers, as it has a marked influence on the price of mink pelt (Liu et al., 2017). This estimated negative genetic correlation between ELISA-G and HL suggested that the mink farmers could select mink with low anti-AMDV antibody level to increase the harvest length of mink, and therefore, reduce the economic losses caused by AD on the body length. To the best of our knowledge, this is the first study that estimated the genetic correlation between ELISA score and body length of mink at harvest. However, the genetic correlations between ELISA test and growth traits were estimated in other species. In laying hens, the ELISA test for Newcastle disease showed a moderate negative genetic correlation (-0.45) with the post Newcastle disease virus challenge growth rate (Rowland et al., 2018), which was the same as our estimate (-0.45). In swine, the ELISA test for PRRS showed a moderate negative genetic correlation (-0.33) with post-infection weight gain (Hess et al., 2018). The different pathogeneses of the disease virus, nature of the animal response to the virus, breeding structures, and statistical models are the potential reasons that lead to some inconsistencies among these estimations.

3.3.9 ALEUTIAN DISEASE TESTS AND ALEUTIAN DISEASE RESILIENCE

The ELISA-G has the potential to be applied as a good indicator for AD resilient mink genetic selection. Resilience has been defined as an animal's ability to maintain its performance under pathogen exposure (Albers et al., 1987; Bisset & Morris, 1996). An indicator, which is easy to measure and genetically correlated with disease resilience traits,

is required for genetic selection of disease resilient animals (Mulder & Rashidi, 2017). Some immune response, health performance, reproduction, and production traits were treated as disease resilience traits for several diseases in farm animals. For example, immune response, health score, feed intake, and litter size were regarded as the disease resilience traits for PRRS disease in pig (Mulder & Rashidi, 2017; Rahe & Murtaugh, 2017; Chen et al., 2020; Cheng et al., 2020). Aleutian disease infected mink is characterized by anemia (McGuire et al., 1979), poor reproduction (Henson et al., 1962; Reichert & Kostro, 2014), gradual body size loss (Kowalczyk et al., 2019), and poor pelt quality (Farid & Ferns, 2011). Therefore, PCV, reproductive performance (female), pelt quality, and harvest length could be regarded as AD resilience traits. The ELISA-G showed a moderate heritability (0.39±0.06), a moderate repeatability (0.58±0.04), significant ($P<0.05$) favorable genetic correlations with all litter size traits, PCV, and HL, and non-significant ($P>0.05$) genetic correlations with pelt quality traits and gestation length in this thesis. All these estimated genetic parameters of ELISA-G indicated that the selection of mink with lower AMDV-G ELISA could not only decrease the anti-AMDV antibody level and the extent of anemia but also improve the female reproductive performance and the harvest length of mink without causing adverse influences on pelt quality and gestation length in AD epidemic ranches. Therefore, ELISA-G could be employed as a good indicator in genetic selection for AD resilient mink in AD epidemic mink ranches.

3.4 CONCLUSIONS

Aleutian disease is a global problem for the mink industry causing severe economic losses and serious animal welfare issues. Genetic selection of AD resilient mink provides a potential method to the mink industry to cope with the adverse influences caused by AD.

This is the first study of the genetics of AD tests in American mink. In this study, the estimated genetic parameters showed the potential of ELISA-G as a good indicator trait for genetic selection of AD resilient mink in AD epidemic ranches. Genetic selection on ELISA-G test results provides an opportunity for mink farmers to reduce the adverse influences caused by AD, but further studies are required to determine the effectiveness of ELISA-G in mink breeding program.

Table 3.1 Significance of fixed and random effects included in the models for the analysis of Aleutian disease tests, pelt quality, female reproductive performance, packed-cell volume, and harvest length traits in mink.

Traits[1]	Fixed effects					Covariates		Random effects	
	Sex	Color type	Year	Dam age	Number of mating	Age at test	Harvest age	Maternal	Permanent environmental
ELISA-G	*[2]	NS[3]	*	NT	NT[4]	NS	NT	*	*
ELISA-P	NS	NS	NS	NT	NT	NS	NT	*	NS
CIEP	*	NS	NS	NT	NT	*	NT	*	NS
IAT	NS	NS	*	NT	NT	*	NT	NS	NS
NAP	NS	*	NS	NT	NT	NT	NT	NS	NT
QUA	NS	*	*	NT	NT	NT	NT	NS	NT
GL	NT	NS	*	*	*	NT	NT	*	NS
KTB	NT	*	*	*	NS	NT	NT	NS	NS
KLB	NT	*	*	*	*	NT	NT	NS	NS
KL3	NT	NS	*	*	*	NT	NT	NS	NS
KLW	NT	NS	*	NS	NS	NT	NT	NS	NS
PCV	NS	*	*	NT	NT	*	NT	NS	NS
HL	*	*	*	NT	NT	NT	*	NS	NT

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test; NAP = live grade of pelt nap length; QUA = live grade of pelt quality; GL = gestation length; KTB = total number of kits born; KLB = number of kits alive 24-h after birth; KL3 = number of kits alive at 3 weeks of age; KLW = number of kits alive at weaning age; PCV = packed-cell volume; HL= the body length at harvest age.

[2]* = significant ($P<0.05$)

[3]NS = not significant ($P>0.05$)

[4]NT = not tested

Table 3.2 Descriptive statistics for Aleutian disease tests, pelt quality, female reproductive performance, packed-cell volume, and harvest length traits in mink.

Traits[1]	Number of records	Mean	SD	Range	CV (%)
ELISA-G	2,359	2.21	2.49	0 to 7	112.67
ELISA-P	1,152	2.14	2.16	0 to 8	100.93
CIEP	1,127	0.82	0.38	0 to 1	46.34
IAT	1,705	0.57	0.93	0 to 4	163.16
NAP	960	3.34	0.88	1 to 5	26.35
QUA	959	1.98	0.74	1 to 3	37.37
GL	3,652	46.46	4.65	32 to 75	10.01
KTB	4,785	6.60	2.68	1 to 17	40.61
KLB	4,788	5.70	2.59	0 to 14	45.44
KL3	2,343	4.18	2.31	0 to 10	55.26
KLW	2,247	4.21	2.26	0 to 10	53.68
PCV	1,709	55.88	4.37	33 to 69	7.82
HL	844	47.79	4.75	33 to 59	9.94

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test; NAP = live grade of pelt nap length; QUA = live grade of pelt quality; GL = gestation length; KTB = total number of kits born; KLB = number of kits alive 24-h after birth; KL3 = number of kits alive at 3 weeks of age; KLW = number of kits alive at weaning age; PCV = packed-cell volume; HL= the body length at harvest age.

Table 3.3 Estimates of variance components and genetic parameters and their standard errors for Aleutian disease tests, pelt quality, female reproductive performance, packed-cell volume, and harvest length traits in mink.

	Variance components[2]				Genetic parameters[3]			
Traits[1]	σ_a^2±SE	σ_m^2±SE	σ_{pe}^2±SE	σ_e^2±SE	h^2±SE	c_d^2±SE	c_{pe}^2±SE	r^2±SE
ELISA-G	1.78±0.34	0.53±0.17	1.15±0.22	1.58±0.10	0.35±0.06	0.10±0.03	0.23±0.05	0.58±0.04
ELISA-P	2.94±0.47	0.40±0.20	NS[4]	1.60±0.24	0.60±0.07	0.08±0.04	NA[5]	NA
CIEP	0.01±0.01	0.02±0.01	NS	0.11±0.01	0.09±0.07	0.14±0.04	NA	NA
IAT	0.22±0.05	NS	NS	0.65±0.41	0.26±0.05	NA	NA	NA
NAP	0.35±0.05	NS	NT	0.36±0.04	0.50±0.06	NA	NA	NA
QUA	0.17±0.04	NS	NT	0.34±0.03	0.34±0.06	NA	NA	NA
GL	3.81±0.59	0.93±0.38	NS	12.26±0.43	0.22±0.03	0.05±0.02	NA	NA
KTB	0.57±0.13	NS	NS	6.55±0.17	0.08±0.02	NA	NA	NA
KLB	0.45±0.12	NS	NS	6.11±0.17	0.07±0.02	NA	NA	NA
KL3	0.24±0.10	NS	NS	3.49±0.13	0.06±0.03	NA	NA	NA
KLW	0.24±0.09	NS	NS	3.05±0.12	0.07±0.03	NA	NA	NA
PCV	5.06±0.95	NS	NS	9.82±0.66	0.34±0.05	NA	NA	NA
HL	1.92±0.42	NS	NT	2.58±0.30	0.43±0.08	NA	NA	NA

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test; NAP = live grade of pelt nap length; QUA = live grade of pelt quality; GL = gestation length; KTB = total number of kits born; KLB = number of kits alive 24-h after birth; KL3 = number of kits alive at 3 weeks of age; KLW = number of kits alive at weaning age; PCV = packed-cell volume; HL= the body length at harvest age.

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

[3]h^2= heritability from univariate models; c_d^2= proportion of phenotypic variance explained by the maternal effects; c_{pe}^2= proportion of phenotypic variance explained by the permanent environmental effects; r^2= repeatability

[4]NS = not significant (P>0.05)

[5]NA = not applicable

Table 3.4 Estimates of heritabilities (diagonal), genetic (below diagonal) and phenotypic (above diagonal) correlations, and their standard errors among Aleutian disease test traits.

Trait[1]	ELISA-G	ELISA-P	CIEP	IAT
ELISA-G	**0.39±0.06**	**0.83±0.01**	**0.26±0.03**	**0.42±0.03**
ELISA-P	**0.99±0.01**	**0.61±0.07**	**0.34±0.03**	**0.42±0.02**
CIEP	0.33±0.20	**0.63±0.18**	0.11±0.07	**0.17±0.03**
IAT	**0.83±0.07**	**0.73±0.08**	**0.48±0.22**	**0.26±0.05**

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test.

[2] The significant (P<0.05) estimates were bolded.

Table 3.5 Estimates of phenotypic correlations and their standard errors between Aleutian disease tests with pelt quality, female reproductive performance, packed-cell volume, and harvest length traits in mink.

Traits[1]	ELISA-G	ELISA-P	CIEP	IAT
NAP	-0.04±0.04	-0.08±0.05	-0.05±0.04	**-0.09±0.04**
QUA	-0.03±0.04	-0.06±0.04	0.01±0.04	-0.06±0.04
GL	0.06±0.05	0.16±0.09	**-0.37±0.09**	-0.10±0.10
KTB	0.03±0.05	-0.10±0.10	**0.44±0.09**	-0.03±0.10
KLB	0.02±0.05	-0.13±0.09	**0.38±0.10**	-0.01±0.10
KL3	-0.09±0.05	-0.13±0.11	0.20±0.11	-0.07±0.09
KLW	**-0.14±0.05**	-0.14±0.09	0.12±0.12	-0.08±0.10
PCV	**-0.33±0.03**	**-0.37±0.03**	**-0.10±0.03**	**-0.32±0.03**
HL	**-0.30±0.06**	-0.03±0.04	-0.09±0.05	-0.07±0.04

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test; NAP = live grade of pelt nap length; QUA = live grade of pelt quality; GL = gestation length; KTB = total number of kits born; KLB = number of kits alive 24-h after birth; KL3 = number of kits alive at 3 weeks of age; KLW = number of kits alive at weaning age; PCV = packed-cell volume; HL= the body length at harvest.

[2] The significant (P<0.05) estimates were bolded.

Table 3.6 Estimates of genetic correlations and their standard errors between Aleutian disease tests with pelt quality, female reproductive performance, packed-cell volume, and harvest length traits in mink.

Traits[1]	ELISA-G	ELISA-P	CIEP	IAT
NAP	-0.20±0.11	-0.20±0.11	-0.35±0.24	**-0.39±0.12**
QUA	-0.02±0.12	0.06±0.14	0.15±0.27	0.19±0.16
GL	-0.18±0.13	-0.02±0.21	-0.51±0.34	-0.10±0.23
KTB	**-0.41±0.16**	-0.37±0.26	0.23±0.58	-0.33±0.31
KLB	**-0.43±0.18**	-0.37±0.27	-0.20±0.62	-0.07±0.33
KL3	**-0.43±0.13**	-0.36±0.23	-0.11±0.56	0.01±0.32
KLW	**-0.49±0.12**	**-0.48±0.24**	-0.29±0.55	-0.01±0.30
PCV	**-0.53±0.09**	**-0.40±0.10**	-0.10±0.24	**-0.56±0.10**
HL	**-0.45±0.16**	-0.02±0.13	0.32±0.29	-0.16±0.16

[1]ELISA-G = AMDV-G based enzyme-linked immunosorbent assay test; ELISA-P= VP2 based enzyme-linked immunosorbent assay test; CIEP = counterimmunoelectrophoresis test; IAT = Iodine agglutination test; NAP = live grade of pelt nap length; QUA = live grade of pelt quality; GL = gestation length; KTB = total number of kits born; KLB = number of kits alive 24-h after birth; KL3 = number of kits alive at 3 weeks of age; KLW = number of kits alive at weaning age; PCV = packed-cell volume; HL= the body length at harvest.

[2] The significant ($P<0.05$) estimates were bolded.

CHAPTER 4 : GENERAL DISCUSSION AND CONCLUSION

4.1 SUMMARY AND GENERAL DISCUSSION

Finding the practical solutions to control Aleutian disease (**AD**) has become a top priority for the fur industry, as AD is causing the significant economic losses and animal welfare issues, and the traditional non-selection control methods (vaccination, medical treatment, and culling) are not able to cope with the adverse effects of AD. Selection for AD resilient mink provides a potential method to the mink industry to control this untreatable disease and reduce the adverse effects of AD on reproduction and production. Some mink farmers are trying to select AD resilient mink based on the phenotypic information of AD tests result, however, the genetic analysis of AD tests and their correlations with pelt quality, reproductive performance, the extent of anemia, and harvest length traits have not been investigated in mink. In other words, the feasibility of genetic selection for AD resilient mink based on the AD tests result had not been verified. Consequently, understanding the genetic and phenotypic parameters of AD tests and their correlations with pelt quality, female reproductive performance, the extent of anemia, and harvest length traits in mink could help mink breeders to implement a successful breeding program for improved AD resilient.

In this thesis, data on 5,824 mink in CCFAR were used to estimate the genetic and phenotypic parameters of two systems of enzyme-linked immunosorbent assay (**ELISA**) systems (antigen-based (**ELISA-G**) and virus capsid protein-based (**ELISA-P**)), counterimmunoelectrophoresis test (**CIEP**), and iodine agglutination test (**IAT**), and their

genetic and phenotypic correlations with pelt quality, female reproductive performance, packed-cell volume (**PCV**), and harvest length (**HL**). Estimated heritabilities (±SE) were 0.39±0.05, 0.61±0.07, 0.11±0.07, and 0.26±0.05 for antigen-based ELISA, virus capsid protein-based ELISA, CIEP, and IAT, respectively. The moderate-to-high heritabilities of both ELISA tests and IAT indicated that these AD tests could be genetically improved through traditional genetic selection. As for CIEP, the low heritability of CIEP indicated the ineffectiveness of selection for CIEP by traditional genetic selection, as the phenotypic observations of CIEP are not good indicators of breeding values and longer time will be needed to genetically improve this trait. The ELISA-G also showed a moderate repeatability (0.58±0.04), which indicated that mink with low ELISA-G tends to remain low in the future.

All the genetic correlations among AD test traits were significant ($P<0.05$) except for the genetic correlation between ELISA-G and CIEP (0.33±0.20). High genetic correlation between ELISA-G and ELISA-P (0.99±0.01) indicated that both measured the same phenotype of anti-AMDV antibody level in this mink population, although they were designed based on different mechanisms. The IAT showed significant ($P<0.05$) high genetic correlations with both ELISA tests (0.83±0.07 and 0.73±0.08 with ELISA-G and ELISA-P, respectively) and a moderate genetic correlation with CIEP (0.48±0.22). These significant ($P<0.05$) genetic correlations indicated that selection of mink with lower IAT scores could indirectly reduce the level of anti-AMDV antibody in mink.

This thesis is the first study to estimate the genetic correlations between AD tests and other traits that are influenced by AD. Except for the significant ($P<0.05$) unfavorable genetic correlation (-0.39±0.12) between IAT and the nap length of pelt (**NAP**), all other AD-

specific tests (ELISA-G, ELISA-P, and CIEP) did not show significant (P<0.05) genetic correlations with pelt quality traits. This indicated that the selection of mink with lower scores of ELISA-G or ELISA-P and negative results of CIEP test would not cause adverse effects on the pelt quality. The ELISA-G was the only AD test with significant (P<0.05) genetic correlations with litter size traits (-0.41±0.16, -0.43±0.18, -0.43±0.13, -0.49±0.12 with total number of kits born, number of kits alive 24-h after birth, number of kits alive at 3 weeks of age, and number of kits alive at weaning age (**KLW**), respectively). These significant (p<0.05) negative genetic correlations indicated that the selection of female mink with lower ELISA-G score could improve the little size of dam. Except for CIEP, all the other AD tests (ELISA-G, ELISA-P, and IAT) showed significant (P<0.05) moderate negative genetic correlations with PCV (-0.53±0.09, -0.40±0.10, and -0.56±0.10, respectively). This indicated that selecting mink with lower scores of ELISA-G, ELISA-P, or IAT could increase the level of red blood cells in blood. The ELISA-G was the only AD test that showed a significant (P<0.05) negative correlation (-0.45±0.16) with harvest length (**HL**), which indicate the selection of mink with lower ELISA-G score could increase the body length of mink at harvest.

4.2 GENERAL CONCLUSIONS AND IMPLICATIONS IN MINK INDUSTRY

The findings in this thesis indicated that ELISA-G could be a good indicator for genetic selection of AD-resilient mink. The moderate heritability (0.39±0.06) and repeatability (0.58±0.04) of ELISA-G and its significant (P<0.05) favorable genetic correlations with litter size traits, PCV, and HL and non-significant (P>0.05) genetic correlations with pelt

quality traits and gestation length indicated that the genetic selection of mink with lower ELISA-G scores could not only decrease the anti-AMDV antibody level and anemia but also improve the female reproductive performance and the harvest length of mink without causing adverse effects on pelt quality and gestation length in AD epidemic ranches. Therefore, the mink farmers could include ELISA-G test as a reliable indicator for AD resilient mink in their genetic selection programs to reduce the economic losses caused by AD. In the current situation that the other methods (e.g., culling strategies, vaccine, and medical treatment) cannot effectively control this disease, genetic selection of AD resilient mink based on ELISA-G test could become the main force in controlling AD. The ELISA-P was not suggested as the indicator to select for AD resilient mink because it did not show a good repeatability as ELISA-G and did not show as many significant ($P<0.05$) genetic correlations with AD resilience traits as ELISA-G. However, high heritability of ELISA-P (0.61 ± 0.07) and its significant ($P<0.05$) genetic correlations with KLW and PCV (-0.48 ± 0.24 and -0.40 ± 0.10, respectively) indicated that ELISA-P test could also be used in genetic selection programs to lower anti-AMDV antibody level and anemia and increase the KLW in AD positive farms.

The findings in this thesis also indicated that CIEP and IAT might not be the suitable tests for selecting AD resilient mink. Low heritability (0.11 ± 0.07) of CIEP and its non-significant ($P>0.05$) genetic correlations with all AD resilience traits showed that CIEP is not a good indicator to select for AD resilient mink. The IAT could be applied as a more economical and convenient test to help mink farmers indirectly select mink with low level of anti-AMDV antibodies and less extent of anemia because IAT is a simple and inexpensive test and showed significant ($P<0.05$) positive genetic correlations with other

AD-specific tests (0.83±0.07, 0.73±0.08, and 0.48±0.22 with ELISA-G, ELISA-P, and CIEP, respectively) and negative genetic correlation with PCV test (-0.32±0.03). However, the significant ($P<0.05$) unfavorable genetic correlation (-0.39±0.12) between IAT and NAP showed that selection for lower IAT would lead to the longer nap length of pelt and decrease the financial income of mink farmers. This is due to the higher market values of short-napped pelts compared to the long-napped pelts (Ward, 2016). Meanwhile, IAT did not show significant ($P<0.05$) genetic correlations with female reproductive performance, HL, and pelt quality traits, which were considered as AD resilient traits. Therefore, CIEP and IAT are not suitable indicators for genetic selection of AD resilient mink.

This is the first comprehensive study of the genetics of AD tests in American mink. The estimates of genetic and phenotypic parameters for AD tests traits in mink not only provided insight into the biological basis of these traits but also a valuable reference to develop the efficient AD-test based genetic programs to help mink farmers to cope with the adverse effects of AD. The findings of this thesis provide a potential method to the mink industry to control AD and reduce the economic losses caused by AD, but further studies are required to determine the effectiveness of ELISA-G in mink breeding programs.

4.3 GENERAL RECOMMENDATIONS

a) The effectiveness of ELISA-G in the mink breeding programs has not been determined. Therefore, routine estimation of the rate of the genetic gain by ELISA-G breeding programs is needed to monitor its effectiveness.

b) Also, the future estimations of genetic correlations between AD tests and other economically important traits such as feeding efficiency, dried pelt quality, and kit

mortality traits could help mink breeders to develop a more comprehensive breeding program for controlling AD.

c) In addition, the genetic and phenotypic parameters in this thesis were estimated by applying traditional BLUP animal models. The availability of genomic information and statistical methods such as GBLUP, ssGBLUP, and Bayesian approaches, provide the opportunities to estimate the genetic and phenotypic parameters of AD tests and their correlations with AD resilient traits and compare the results with the current results. This would help mink breeders to use the new technologies for development of breeding programs using more accurate methods.

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APPENDIX 1. STATUS OF MANUSCRIPTS SUBMITTED FROM THE MASTER'S THESIS (AS OF 22 FEBRUARY 2021)

1. Based on **Chapter 2**
   Hu, G., Do, D. N., Gray, J., & Miar, Y. (2020). Selection for Favorable Health Traits: A Potential Approach to Cope with Diseases in Farm Animals. **PUBLISHED in Animals**, 10(9), 1717.

2. Based on **Chapter 3**
   Hu, G., et al. (2021). Genetic and phenotypic parameters for Aleutian disease tests and their correlations with pelt quality, reproductive performance, packed-cell volume, and harvest length in mink. **WILL BE SUBMITTED** to **Journal of Animal Science**.

APPENDIX 2. ENZYME-LINKED IMMUNOSORBENT ASSAY TEST

Figure A2.1 Blood sample comb for enzyme-linked immunosorbent assay test

APPENDIX 3. IODINE AGGLUTINATION TEST

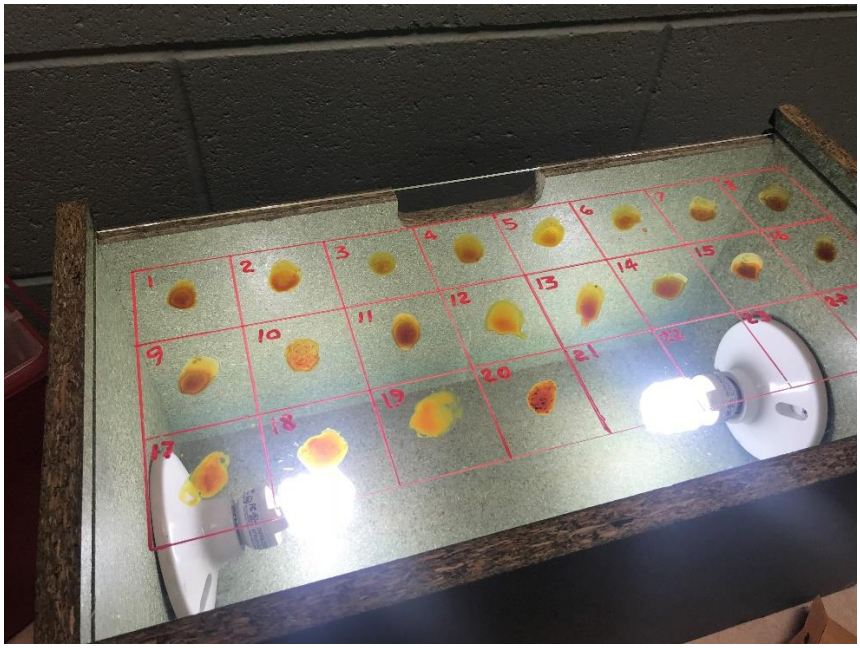


Figure A3.1 Iodine agglutination test results

APPENDIX 4. PACKED-CELL VOLUME TEST

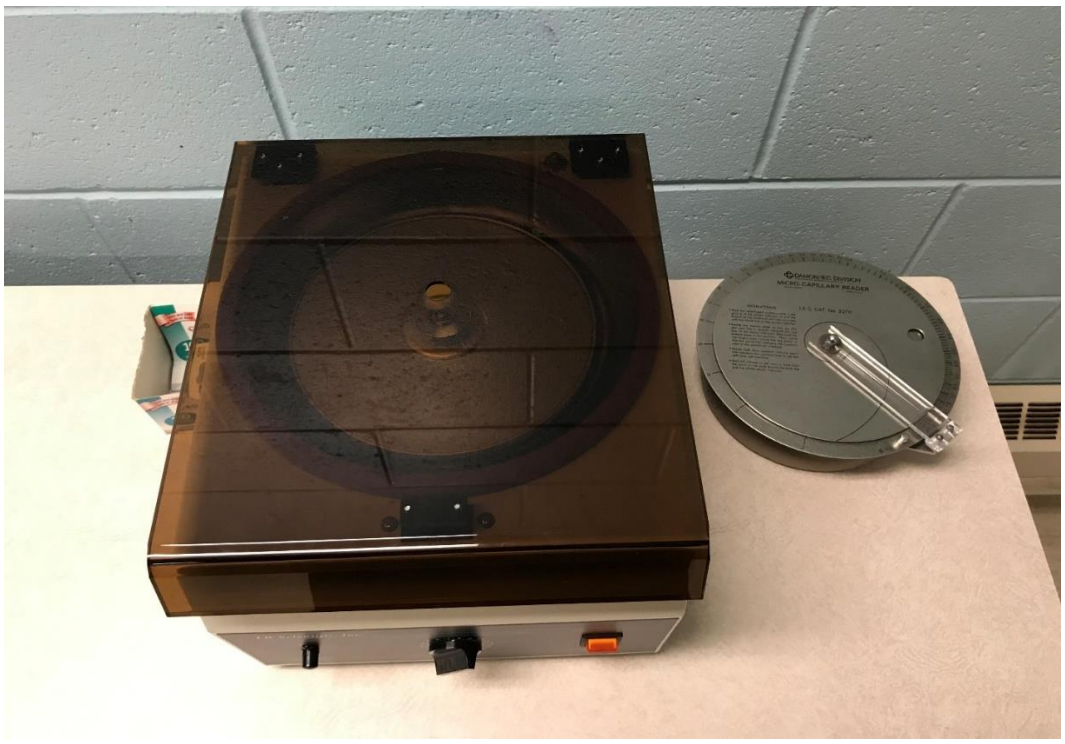


Figure A4.1 Centrifuge and hematocrit reader used for packed-cell volume test

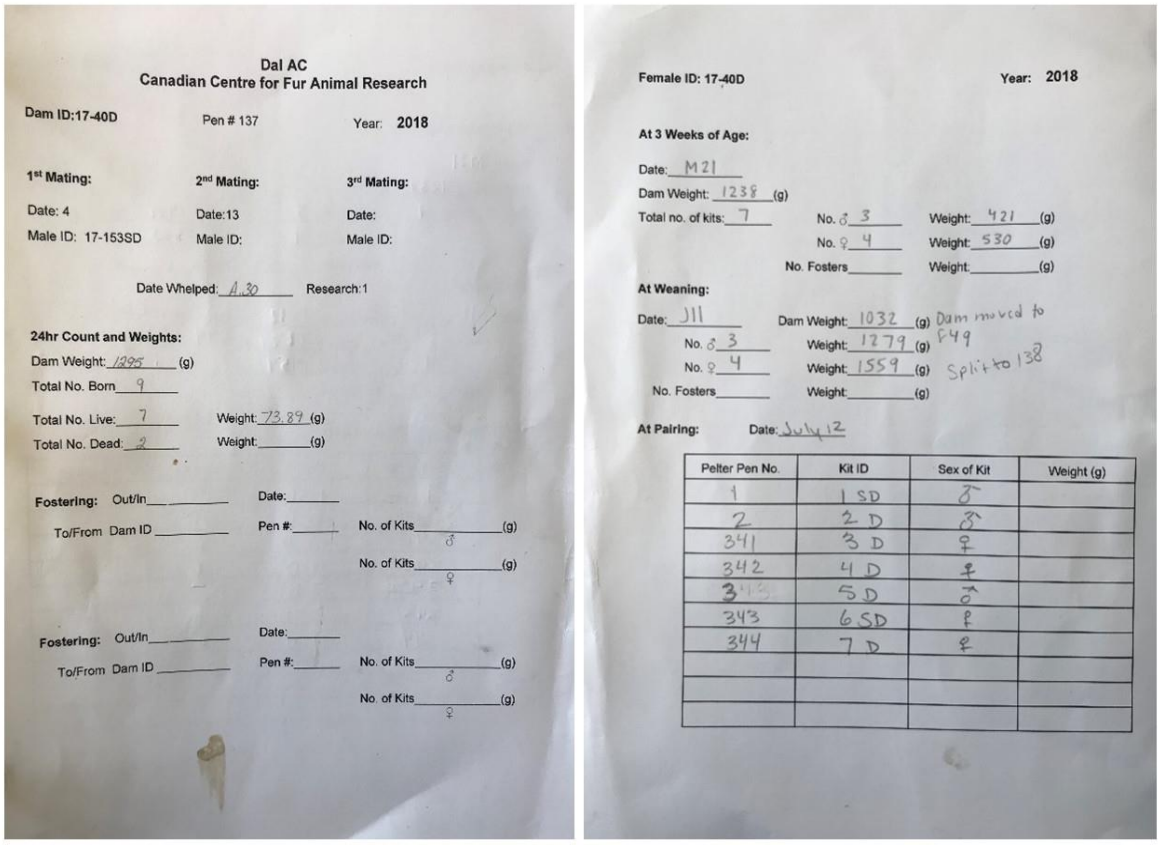
APPENDIX 5. HARVEST LENGTH MEASUREMENT

Figure A5.1 The measurement board used to measure the harvest body length of mink

APPENDIX 6. REPRODUCTIVE PERFORMANCE RECORD

Figure A6.1 The total number of newborn kits born and the dam

Figure A6.2 The total number of newborn kits that survived 24-hr after birth of a dam



Dal AC
Canadian Centre for Fur Animal Research

Dam ID:17-40D Pen # 137 Year: 2018

1st Mating: 2nd Mating: 3rd Mating:
Date: 4 Date:13 Date:
Male ID: 17-153SD Male ID: Male ID:

Date Whelped: A.30 Research:1

24hr Count and Weights:
Dam Weight: 1295 (g)
Total No. Born 9
Total No. Live: 7 Weight: 73.89 (g)
Total No. Dead: 2 Weight: (g)

Fostering: Out/In Date:
To/From Dam ID Pen #: No. of Kits (g) ♂
No. of Kits (g) ♀

Fostering: Out/In Date:
To/From Dam ID Pen #: No. of Kits (g) ♂
No. of Kits (g) ♀

Female ID: 17-40D Year: 2018

At 3 Weeks of Age:
Date: M 21
Dam Weight: 1238 (g)
Total no. of kits: 7 No. ♂ 3 Weight: 421 (g)
No. ♀ 4 Weight: 530 (g)
No. Fosters Weight: (g)

At Weaning:
Date: J11 Dam Weight: 1032 (g) Dam moved to P49
No. ♂ 3 Weight: 1279 (g)
No. ♀ 4 Weight: 1559 (g) Split to 138
No. Fosters Weight: (g)

At Pairing: Date: July 12

Pelter Pen No.	Kit ID	Sex of Kit	Weight (g)
1	1 SD	♂	
2	2 D	♂	
341	3 D	♀	
342	4 D	♀	
3[illegible]	5 D	♂	
343	6 SD	♀	
344	7 D	♀	

Figure A6.3 The reproduction record forms in Canadian Centre for Fur Animal Research