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Familial disease history and fur color type are associated with urinary tract disease in farmed mink (Neovison vison)

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1. Introduction

Mink urinary tract disease (MUTD) and mink fatty liver disease (MFLD) are often asymptomatic and develop rapidly to fatal disease (Bjornvad et al., 2004; Hunter and Lemieux, 1996; Mundbjerg et al., 2020; Rouvinen-Watt et al., 2010), thus the focus needs to be on preventative measures rather than treatment. Studies of heritability and genetic predisposition to MUTD and MFLD have been impaired by the rapid progression of disease entities and the fact that the disease is often diagnosed at the post mortem examination (Clausen, 2006; Hansen et al., 2007; Mundbjerg et al., 2020). Also because mortality associated with MUTD and MFLD most often occur in young immature mink, a potential genetic predisposition will not be passed on directly by the animals itself, but potentially by relatives.

MUTD is a disease entity of postweaning mink kits characterized by urolithiasis, cystitis and/or pyelonephritis leading to mortality (Mundbjerg et al., 2020; Nielsen, 1956). Necropsies of mink have shown that urolithiasis, cystitis and pyelonephritis often occur simultaneously, with the most commonly recorded type of urolith reported being struvite stones (Leoschke et al., 1952; Nielsen, 1956; Sompolskiny, 1950). Mortality is attributed to lower urinary tract obstruction, similar to what is reported for lower urinary tract disease (LUTD) in felines (Gerber et al., 2005). MUTD has been associated with mortality in farmed mink for the past sixty years, but the epidemiology and pathogenesis of the disease remains unelucidated (Clausen, 2006; Nielsen, 1956; Sompolskiny, 1950; Witte and Zimmermann, 1985). In farmed mink MUTD has been reported in male kits from 2 to 6 months of age and also in adult females (Clausen, 2006; Nielsen, 1956; Sompolskiny, 1950). There are multiple studies suggesting heritability and familial aggregation of urolithiasis in humans (Curhan et al., 1999; Hemminki et al., 2018;
MFLD is also reported to be a significant cause of mortality in growing mink kits (Clausen, 2006; Hunter and Lemieux, 1996). In mink, MFLD presents as severe hepatic steatosis and has been induced by fasting in obese animals (Dick et al., 2014; Rouvinen-Watt et al., 2010). Mink with MFLD spontaneously develop severe hepatic steatosis (Dick et al., 2014; Rouvinen-Watt et al., 2010). The hepatic steatosis of MFLD is similar to non-alcoholic fatty liver disease (NAFLD) in humans. MFLD exhibits a rapid onset of hepatic steatosis and the biochemical and molecular manifestations of the food-deprivation induced disease have significant similarities to the human NAFLD induced by obesity (Rouvinen-Watt et al., 2010) and it has been suggested that the mink may represent an interesting model organism for NAFLD. Evidence of heritability of NAFLD in humans has been provided by epidemiological, familial, and twin studies (Guerrero et al., 2009; Makkonen et al., 2009; Schwimmer et al., 2009; Struben et al., 2000; Willner et al., 2001).

There is considerable variation in the prevalence and impact of MUTD and MFLD between farms sharing the same housing and feed kitchen (Hansen et al., 2007; Mundbjerg et al., 2020). Additionally, specific color types of mink have proven to be associated with increased susceptibility to diseases (Hegreberg et al., 1969; Jespersen et al., 2017; Tung et al., 1981). It is speculated that increased genetic susceptibility in some genotypes or strains of mink may be part of the explanation for variation in mortality between farms.

The aim of this study was to investigate familial aggregation of MUTD and MFLD leading to mortality in mink, by testing the hypothesis that family history of MUTD or MFLD significantly increased risk of the conditions leading to mortality in mink kits. Also, associations between disease and color type (brown and black) and sex were assessed within the study population.

2. Material and methods

The initial data of our prospective cohort study included all mink housed on Danish Fur Breeders Research Center during the years 2012 to 2015 (n = 63,110) and their complete data from Kopenhagen Fur’s breeding database.

The diagnosis of MUTD and MFLD was made by systematic post mortem examination by the farm veterinarian of all animals found dead. Post mortem diagnosis of MUTD was made if the primary post mortem finding was lesions of lower urinary tract obstruction including acute hemorrhagic urocystitis (overdistended bladder with hemorrhagic or purulent contents and edema and/or hemorrhagic of the bladder mucosa), urolithiasis and/or pyelonephritis (enlargement of the kidneys, accumulations of suppurative or hemorrhagic exudate and/or uroliths in the renal pelvis). Post mortem diagnosis of MFLD was made if the primary post mortem finding was hepatic steatosis, characterized by hepatomegaly, with diffuse light discoloration and reduced texture. In order to minimize inclusion of kidney lesions and hepatic steatosis secondary to other diseases, only diagnoses made within the first year after birth were included.

To ensure complete data availability for all animals within the study population only mink kits with known familial history, records of unique ID for both parent animals and known sex were included. Consequently, first generation mink kits of purchased breeders (n = 16,931) or of breeders with invalid/unknown unique ID number (insufficient registration, n = 3500) were excluded due to unknown familial disease history. The complete data processing for study population establishment is illustrated in Fig. 1.

The final study population included all mink kits housed on Danish Fur Breeders Research Center during the years 2013 to 2015 (n = 27,511), with parents also born on these facilities in Holstebro, Denmark. A total of 21,938 (79.7%) mink kits were of the color type brown and 5573 (20.3%) were black mink.

All dead and euthanized mink in the study period were examined with standardized necropsy procedures performed by the farm veterinarian to establish cause of death. Mink diagnosed post mortem with...
urolithiasis, cystitis and/or nephritis were recorded combined as MUTD. Mink kits with a unique animal ID within the defined study population with MUTD (n = 221) or MFLD (n = 138) were identified. The data process is illustrated in Fig. 2.

Data regarding litter, sire (father) and dam (mother) of all mink kits within the study population were obtained from Kopenhagen Fur’s breeding database. During statistical analysis all mink kits not diagnosed post mortem with the disease in question (MUTD or MFLD) were defined as healthy.

2.1. Statistical analysis

The method for familial aggregation analysis and definition of familial history was motivated by Zimmerman et al., 2009. Chi square tests with Yates’ continuity correction were used to investigate the association between prevalence of MUTD and MFLD in mink kits and family history of disease. Family history was defined as MUTD or MFLD leading to mortality in siblings of the dam or sire. Exploratory analyses of the association between MUTD and family history was also carried out for mink of color type black and brown separately. Additionally, associations between prevalence of disease and the variables sex and color type were tested using Chi square tests. We report estimates and 95% confidence intervals (CI) for the prevalence of disease. The relative risk (RR) and 95% confidence intervals were computed to quantify differences in prevalence of disease between groups. Statistical analyses were carried out using R, in particular calculation of CIs for RR was based on the “riskratio” function from the “fmsb” package.

3. Results

The study population included a total of 27,511 mink with 221 being diagnosed post mortem with MUTD resulting in an overall prevalence of 0.8% [CI: 0.7–0.9%]. The prevalence of MUTD was significantly higher (p < 0.001) in black mink (1.6% [CI: 1.3–1.9%]) than in mink of brown color type (0.6% [CI: 0.5–0.7%]). The distribution of mink with a post mortem diagnosis of MUTD and familial history of MUTD is presented in Table 1.

There was a significant association between mink kits with MUTD post mortem and their family being diagnosed with MUTD post mortem which confirmed the presence of familial aggregation (p = 0.012). A mink kit with family diagnosed with MUTD had 1.7 (CI: 1.1–2.4) times higher probability of being diagnosed itself compared to mink from healthy families.

A total of 138 mink kits were diagnosed post mortem with MFLD resulting in an overall prevalence of 0.5% [CI: 0.4–0.6%]. The prevalence of MFLD was significantly higher (p = 0.03) in black mink (0.7% [CI: 0.5–1.0%]) than in mink of brown color type (0.5% [CI: 0.4–0.6%]). The distribution of mink with a post mortem diagnosis of MFLD and familial history of MFLD is presented in Table 2.

<table>
<thead>
<tr>
<th>Family</th>
<th>Mink kit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUTD</td>
<td>Healthy^c</td>
</tr>
<tr>
<td>MUTD^a</td>
<td>30 (1.3%)</td>
<td>2337 (98.7%)</td>
</tr>
<tr>
<td>Healthy^b</td>
<td>191 (0.7%)</td>
<td>24,953 (99.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>221</td>
<td>27,290</td>
</tr>
</tbody>
</table>

^a Defined as siblings of the dam or sire. ^b Mink diagnosed post mortem with urolithiasis, cystitis and/or pyelonephritis. ^c Mink within the study population not diagnosed with MUTD.

Table 2

Distribution of mink kits with and without MFLD (mink fatty liver disease) in relation to family history of fatty disease.

<table>
<thead>
<tr>
<th>Family</th>
<th>Mink kit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MFLD^d</td>
<td>Healthy^e</td>
</tr>
<tr>
<td>MFLD^e</td>
<td>14 (0.9%)</td>
<td>1856 (99.1%)</td>
</tr>
<tr>
<td>Healthy^b</td>
<td>124 (0.5%)</td>
<td>25,517 (99.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>27,373</td>
</tr>
</tbody>
</table>

^d Defined as siblings of the dam or sire. ^e Mink within the study population not diagnosed with MFLD.

Fig. 2. Illustration of the data process identifying mink kits with mink urinary tract disease (MUTD) and mink fatty liver disease (MFLD) within the defined study population.
No significant association between mink kits with MFLD post mortem and their family being diagnosed with MFLD post mortem was found ($p = 0.163$). A mink kit with family diagnosed with MFLD has 1.5 times higher probability of being diagnosed itself compared to mink from healthy families ($RR = 1.5$, CI: $0.9–2.7$).

The post mortem occurrence of both MUTD and MFLD were significantly associated with sex and color type. Results are listed in Table 3. With a relative risk of 2.6 the mink color type black had more than twice the probability of having the post mortem diagnosis MUTD compared to mink of the color type brown. Male mink had 3.7 times higher probability of dying from MUTD than female mink and 1.9 times higher risk of dying from MFLD.

The relation of mink with MUTD post mortem and their family having MUTD post mortem was investigated in mink of the color type black and brown separately by Chi square tests. In mink of the color type brown there was a significant association between mink kits with MUTD post mortem and their family being diagnosed with MUTD post mortem ($p < 0.001$), but the association was not found in mink of the color type black ($p = 1$). The results presented in Table 3.

4. Discussion

In the four generations of mink included in the research farm data, mink originating from parents having siblings with a history of MUTD diagnosed post mortem, were twice as likely getting this diagnosis (1.3%) than mink originating from healthy families (0.7%). This is to our knowledge the first report of results indicating familial aggregation in relation of MUTD. The findings are in agreement with reports of familial aggregation in both urolithiasis and recurrent cystitis in humans (Hemminki et al., 2018; Hopkins et al., 1999; Stauffer et al., 2004). Our results indicate that by excluding the siblings of mink diagnosed with MUTD from breeding, the farmers may reduce the risk of disease occurrence in the following generation of mink kits.

Familial aggregation of hepatic steatosis is known in humans (Willer et al., 2001) but we did not find familial aggregation of MFLD in this study, though mink originating from families with MFLD were found more likely to be diagnosed with MFLD (0.9%) than mink from healthy families (0.5%). This trend suggests association, though not significant in our study population. A larger study population might reveal familial aggregation. In addition, we investigate one mink farm and to confirm a general validity of the results it would be necessary to include data from more farms in the investigation.

The clustering of disease in close family members may be explained by sharing of either environmental or genetic factors or both and familial aggregation studies estimate the increased risk of disease in relatives of affected probands, or the risk to an individual given his or her family history (Zimmerman et al., 2009). In this context, the family history of disease may be considered a risk factor for a putative susceptibility genotype. While the effect of environmental factor cannot be ruled out completely, they are expected to vary little between individual mink because of standardized housing and management.

In this investigation, mink of the color type black showed significantly higher risk of being diagnosed with MUTD ($RR = 2.6$; CI: 2.0–3.3) and MFLD ($RR = 1.6$; CI: 1.1–2.2) compared to brown mink. Specific color types of mink is known to be genetically linked to immune deficiency and thereby predisposition to disease development including bacterial infections (Leader et al., 1963; Pudgett et al., 1967; Rüt et al., 1972). As MUTD often presents as a combination of urolithiasis and cystitis in mink (Nielsen, 1956; Sompolinsky, 1950; Witte and Zimmermann, 1985) one could speculate that differences in immune competence of color type brown mink would influence development of disease making immune deficient animals more prone to cystitis and thereby urolithiasis. Immune deficiency as a causal factor in development of MUTD in mink needs to be investigated further. The significant difference in MFLD occurrence between color types could indicate some genetic predisposition for disease in black mink despite the lack of familial aggregation. Genetic predisposition for the similar syndrome non-alcoholic hepatic steatosis in humans has been reported (Schwimmer et al., 2009; Struben et al., 2000). Potentially a larger dataset including more farms may reveal similar genetic predisposition in mink.

The increased risk of MUTD in black mink is in agreement with findings of this color type having a higher prevalence of histological lesions in the kidneys, higher kidney weight and higher levels of blood urea than brown mink (Clausen and Hammer, 2016). These data were obtained from the same research farm and within the same timeframe (Clausen 2019, personal communication) as this investigation and thereby on mink of the same genetics. One could speculate if the black mink on the research farm are genetically predisposed to MUTD. The increased risk of MUTD in mink kits with a family history of MUTD was only significant in mink of the color type brown using exploratory statistics. This eliminates the possibility of the found familial aggregation across color types only being an effect of apparently predisposed black mink. In this study we define MUTD by the presence of the lesions in mink kits and that experimentally induced cystitis results in both urolithiasis and pyelonephritis in mink (Nielsen, 1956). Based on this knowledge we analyzed these three lesions as one disease entity. Hence, our results do not clarify if the familial predisposition to MUTD is linked to one, two or all three included urinary lesions.

To establish the study population with known familial history of MUTD and MFLD we excluded all first-generation kits of all purchased breeding animals from the analysis. This approach could select for inbred animals. Struvite urolithiasis has previously been found to have a higher prevalence in inbred than in outbred beagles (Kasper et al., 1978) and we cannot exclude that selection for inbreeding could affect our results.

In this study the overall prevalence of animals with MUTD and MFLD leading to mortality was 0.8% and 0.5%, respectively. In comparison

<table>
<thead>
<tr>
<th>N</th>
<th>Disease in mink kit (n)</th>
<th>Chi Square test</th>
<th>P-value</th>
<th>RR [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>13.834</td>
<td>175</td>
<td>73.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>13.677</td>
<td>46</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Color type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5.573</td>
<td>87</td>
<td>49.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Brown</td>
<td>21.938</td>
<td>134</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>MUTD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.892</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20.046</td>
<td>111</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MUTD family in brown mink</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>475</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>5.098</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MFLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13.834</td>
<td>91</td>
<td>13.0</td>
<td>&lt; 1.9</td>
</tr>
<tr>
<td>Female</td>
<td>13.677</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Color type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5.573</td>
<td>39</td>
<td>5.0</td>
<td>0.025</td>
</tr>
<tr>
<td>Brown</td>
<td>21.938</td>
<td>99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Displaying results of the Chi square test and the relative risk (RR) with confidence interval (CI) when testing occurrence of MUTD and MFLD in mink kits in relation to sex, color type and disease in the family within the colors types brown and black for MUTD.

\[ N \text{ disease in mink kit (n)} \]

\[ \text{Chi Square test} \]

\[ P \text{-value} \]

\[ \text{RR [CI]} \]

\[ \text{a Tested with 1 degrees of freedom at a 95% confidence level.} \]

\[ \text{b Mink diagnosed post mortem with urolithiasis, cystitis and/or pyelonephritis.} \]

\[ \text{c Mink diagnosed post mortem with hepatic steatosis.} \]

\[ \text{d Defined as MUTD diagnosed post mortem in siblings of the dam or sire.} \]
Hansen et al. (2007) found much lower prevalences of urinary tract disease in a study of kit mortality on 10 Danish mink farms, where the highest farm prevalence of recorded was 2.7%. Variations in prevalence of urinary tract disease between farms have previously been reported (Hansen et al., 2007; Mundbjerg et al., 2020). In the previous studies, only mortalities from June/July till October of one production year were included, while the present study includes a longer study period and several generations of mink during a three-year period. Hansen et al. (2007) found significant variation in the prevalence of fatty liver between farms. The prevalence found in our investigation is within the range reported in previous studies, supporting the assumption that disease occurrence on the research farm can be considered representative.

MUTD has been reported to cause mortality more often in male than female mink kits (Clausen, 2006; Mundbjerg et al., 2020; Sompolinsky, 1950). In this study male mink presented a 3.7 times higher risk of MUTD than females. Epidemiological investigations of struvite urolithiasis in ferrets found similar results with males being 3.6 times more likely to develop struvite than females and the male anatomy of urethra and os penis is suggested as possible cause (Nwaokorie et al., 2011). This could also apply for mink as the two species share the anatomical feature of the j-shaped os penis (Elder, 1951; Orcutt, 2003). Male mink also have twice the risk (RR = 1.9) of post mortem MFLD compared to females. Male mink are bigger and consume more feed than female mink (Dick et al., 2014). Farm mink have been genetically selected for a large body frame (Lassen et al., 2012) and are capable of storing larger quantities of body fat. This may contribute to a higher mortality caused by MFLD in male mink kits.

Our method of combining disease data with breeding data in mink kits for studies of heredity and family aggregation could potentially be a tool for breeding more robust and healthy farm mink. The approach used in this study could be applied for the analysis of other diseases causing mortality in mink and may be applied to all farms collecting the relevant data, thereby allowing for improved breeding management and selective breeding for increased robustness and health in the farm mink. The main obstacle for such further studies is poor records of disease and causes of death on mink farms. While records of treatment and mortality data are recorded with animal ID, which was a necessary basis for this study. Our purpose with this study was to investigate simple family connections which would be applicable in current farm selection practice where breeding programs are infrequently used. Using more sophisticated methods it would be possible to investigate more complex family relations with calculation of heredity estimates, but this was beyond the scope and resources for this study.

To our knowledge this is the first report of data indicating familial aggregation of MUTD in mink farm. In addition, we found a higher risk of both MUTD and MFLD in male mink and in mink of the color type black when compared to brown. The data investigated in our analysis only represent one Danish farm which is a clear limitation of our study in terms of general validity. The results of this study emphasize the need for more systematic records of disease and mortality on mink farms. Technological development including digital data recording apps combined with bar code numbers on the cages may facilitate such data collection in the future.

Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

None.

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References


