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Research paper

The influence of age and genetics on natural resistance to experimentally induced feline infectious peritonitis

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ABSTRACT

Naturally occurring feline infectious peritonitis (FIP) is usually fatal, giving the impression that immunity to the FIP virus (FIPV) is extremely poor. This impression may be incorrect, because not all cats experimentally exposed to FIPV develop FIP. There is also a belief that the incidence of FIP may be affected by a number of host, virus, and environmental cofactors. However, the contribution of these cofactors to immunity and disease incidence has not been determined. The present study followed 111 random-bred specific pathogen free (SPF) cats that were obtained from a single research breeding colony and experimentally infected with FIPV. The cats were from several studies conducted over the past 5 years, and as a result, some of them had prior exposure to feline enteric coronavirus (FECV) or avirulent FIPVs. The cats were housed under optimized conditions of nutrition, husbandry, and quarantine to eliminate most of the cofactors implicated in FIPV infection outcome and were uniformly challenge exposed to the same field strain of serotype 1 FIPV. Forty of the 111 (36%) cats survived their initial challenge exposure to a Type I cat-passaged field strains of FIPV. Six of these 40 survivors succumbed to FIP to a second or third challenge exposure, suggesting that immunity was not always sustained. Exposure to non-FIP-inducing feline coronaviruses prior to challenge with virulent FIPV did not significantly affect FIP incidence but did accelerate the disease course in some cats. There were no significant differences in FIP incidence between males and females, but resistance increased significantly between 6 months and 1 or more years of age. Genetic testing was done on 107 of the 111 infected cats. Multidimensional scaling (MDS) segregated the 107 cats into three distinct families based primarily on a common sire(s), and resistant and susceptible cats were equally distributed within each family. Genome-wide association studies (GWAS) on 73 cats that died of FIP after one or more exposures (cases) and 34 cats that survived (controls) demonstrated four significant associations after 100k permutations. When these same cats were analyzed using a sib-pair transmission test, three of the four associations were confirmed although not with genome-wide significance. GWAS was then done on three different age groups of cases to take into account age-related resistance, and different associations were observed.

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The only common and strong association identified between the various GWAS case configurations was for the 34.7–45.8 Mb region of chromosome A3. No obvious candidate genes were present in this region.

1. Introduction

The prevalence and severity of infectious diseases among multi-cat populations is a product of many diverse factors that affect the host/pathogen interaction (Pedersen, 1991). Environmental factors include things such as population density, sanitation, and interchange of animals while agent factors include virulence, dose, and route of exposure. Host factors include developmental and heritable anomalies in the immune system and age at the time of exposure and intercurrent illnesses. Many of these diverse cofactors have been implicated in FIP.

Foley et al. (1997) studied a number of environmental risk factors for FIP in seven catteries and found that cat numbers (density) and husbandry procedures had no influence on FIP incidence while age, high coronavirus antibody titers, and the proportion of cats shedding coronavirus were significantly associated with FIP risk. All of these risk factors are interrelated, because fecal coronavirus shedders are much more likely to have antibody titers >1:100 and younger cats are more likely to shed FECV at higher levels and for longer periods (Pedersen et al., 2004, 2008). The stresses of placing young cats into shelters have also been shown to greatly increase the levels of FECV shedding (Pedersen et al., 2004).

Field strains of FIPV are known to vary intrinsically in virulence and this virulence may be further affected by the route of administration (Pedersen et al., 1984; Pedersen and Floyd, 1986). The dose of virus used also can alter disease outcome although a dose that causes lethal infection in one cat may be insufficient to infect another (Pedersen and Black, 1983). Virulence may be influenced by the exact FIP-inducing mutations that are present. The known FIP-associated mutations in FECV 3c and the S1/S2 cleavage site are highly variable and unique to each isolate while the two single nucleotide mutations in the fusion domain are common to all FIPVs (Pedersen, 2014). Mutations in 7b can also alter virulence in some tissue culture-adapted strains, but do not play a role in the FECV-to-FIPV mutations in nature (Pedersen, 2014). Additional mutations may await discovery and their singular or collective roles in FIP remain to be determined.

Several host factors have been implicated in FIP. The stress of surgery, especially when performed at a young age, may increase susceptibility of cats to FIP development (Kass and Dent, 1995). Co-infections with FeLV will greatly increase the incidence of FIP by interfering with FIP immunity; more than one-third of all FIP cases occurred in cats that were persistently infected with FeLV (Cotter et al., 1973; Pedersen et al., 1977). Feline immunodeficiency virus (FIV) can also compromise host immunity and increase FIP prevalence under experimental conditions (Poland et al., 1996).

The present study was designed to eliminate as many potential agents, environmental, and host risk factors for FIPV infection as possible. The same field strain and infectious dose of virus were used for challenge exposure, a uniform standard of care was provided with no extraneous pathogen exposure, and the cats originated from the same breeding stock. The study was then concentrated on two potential risk factors that have been poorly studied, age at the time of exposure and genetic susceptibility.

The effect of age on FIPV infection has not been directly addressed, even though it has been previously discussed (Pedersen, 2009) and well documented for pathogens such as feline leukemia virus (FeLV) (Hoover et al., 1976). Kittens are born with immature immune systems, and the period between 4 and 16 weeks of age is when IgG and IgA systems are being compensated by passive local and systemic immunity (Pedersen, 1987a). Immaturity of the immune system may also play a role in the ability to vaccinate kittens to FIP; a commercially marketed attenuated live FIPV vaccine only demonstrated sufficient efficacy for licensing when given to kittens 16 weeks or older (Gerber et al., 1990). Field and laboratory studies indicate that some sort of maternal or innate resistance to FECV infection is present in neonatal kittens and that FECV fecal shedding usually does not occur until 9 weeks of age, even among kittens born to infected queens (Pedersen et al., 2008). Most cases of FIP occur in cats between 4 and 18 months of age (reviewed Pedersen, 2009) suggesting that some infections may remain subclinical for an extended period of time.

The possible role of genetics in FIP resistance has been implied from a number of studies. FIP did not exist before the 1950s (Holzworth, 1963), suggesting that cats may not have had time to genetically adapt, thus explaining why morbidity and mortality are so high in experimental FIPV infections. Pedigreed cats are more likely to develop FIP than random-bred cats (Robison et al., 1971; Rohrbach et al., 2001; Pesteanu-Somogyi et al., 2006; Worthing et al., 2012), and certain breeds are also more likely to succumb to FIP (Bell et al., 2006; Norris et al., 2005; Pesteanu-Somogyi et al., 2006; Worthing et al., 2012). One study of Persian catteries and pedigrees indicated that susceptibility to FIP was at least 50% heritable (Foley and Pedersen, 1996). Resistance to FIP in Birman cats also appears to have a genetic component as determined by GWAS (Golovko et al., 2013). Natural resistance to FIP has also been observed in up to one-third of random-bred cats used as controls in vaccine studies (Baldwin and Scott, 1997; Gerber et al., 1990; Glansbeek et al., 2002; Hohdatsu et al., 2003; Kiss et al., 2004; Pedersen and Black, 1983; Wasmoen et al., 1995).

The cats, infection outcome data, and DNA used in the present study originated from studies on type 1 FIPV and FECV conducted over the last several years with other objectives. Over the course of these studies, 111 cats of various age and gender were exposed one or more times