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Emerging prion disease drives host selection in a wildlife population

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Abstract. Infectious diseases are increasingly recognized as an important force driving population dynamics, conservation biology, and natural selection in wildlife populations. Infectious agents have been implicated in the decline of small or endangered populations and may act to constrain population size, distribution, growth rates, or migration patterns. Further, diseases may provide selective pressures that shape the genetic diversity of populations or species. Thus, understanding disease dynamics and selective pressures from pathogens is crucial to understanding population processes, managing wildlife diseases, and conserving biological diversity. There is ample evidence that variation in the prion protein gene (PRNP) impacts host susceptibility to prion diseases. Still, little is known about how genetic differences might influence natural selection within wildlife populations. Here we link genetic variation with differential susceptibility of white-tailed deer to chronic wasting disease (CWD), with implications for fitness and disease-driven genetic selection. We developed a single nucleotide polymorphism (SNP) assay to efficiently genotype deer at the locus of interest (in the 96th codon of the PRNP gene). Then, using a Bayesian modeling approach, we found that the more susceptible genotype had over four times greater risk of CWD infection; and, once infected, deer with the resistant genotype survived 49% longer (8.25 more months). We used these epidemiological parameters in a multi-stage population matrix model to evaluate relative fitness based on genotype-specific population growth rates. The differences in disease infection and mortality rates allowed genetically resistant deer to achieve higher population growth and obtain a long-term fitness advantage, which translated into a selection coefficient of over 1% favoring the CWD-resistant genotype. This selective pressure suggests that the resistant allele could become dominant in the population within an evolutionarily short time frame. Our work provides a rare example of a quantifiable disease-driven selection process in a wildlife population, demonstrating the potential for infectious diseases to alter host populations. This will have direct bearing on the epidemiology, dynamics, and future trends in CWD transmission and spread. Understanding genotype-specific epidemiology will improve predictive models and inform management strategies for CWD-affected cervid populations.

Key words: Bayesian modeling; chronic wasting disease (CWD); disease-driven selection; epidemiology; evolution; infection rate; mortality rate; population dynamics; prion disease; single nucleotide polymorphism (SNP); white-tailed deer; wildlife disease.

Introduction

Infectious diseases are one of the important forces driving population dynamics and natural selection in wildlife populations. It has long been recognized that diseases can play a role in population declines and adversely impact sensitive species (McCallum and Dobson 1995). Short of decimating populations, infectious agents may act to constrain population size, growth rates (Anderson and May 1979), and species distributions (Atkinson and LaPointe 2009), and influence migratory escape from pathogens (Altizer et al. 2011). It is well established in agricultural systems (Goldmann 2008) and human populations (Van Blerkom 2003) that adaptation to disease can drive host evolution; but empirical evidence of quantifiable natural selection in free-ranging wildlife populations is rare. Although population studies have identified selection in some systems, it is notoriously difficult to identify specific genetic components under selection and quantify disease-related selective forces (Dwyer et al. 1990). For example, high diversity in major histocompatibility

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complex (MHC) genes has been associated with natural selection for immune response to diverse pathogens (Piertney and Oliver 2006); but seldom is the variation linked to specific pathogen responses (Paterson et al. 1998). In addition, infection rates and population impacts from diseases are particularly difficult to estimate in wild populations (Daszak et al. 2000, McCallum et al. 2001), and evolutionary pressure is difficult to quantify (Altizer et al. 2003*a*).

Chronic wasting disease (CWD), an always fatal neurodegenerative prion disease affecting North American cervids including white-tailed (*Odocoileus virginianus*) and mule deer (*Odocoileus hemionus*), elk (*Cervus canadensis*), and moose (*Alces alces)* (Williams et al. 2002, Baeten et al. 2007), has become a long-term management concern in North America (Spraker et al. 1997). Where CWD is endemic and has risen to high prevalence, this disease has led to decreased survival and declines in deer abundance (Miller et al. 2008). Even in areas of low prevalence, the disease has affected public attitudes toward wildlife resources and has impacted harvest-based revenues of state management agencies (Bishop 2004). The potential long-term threats to wild cervid populations make CWD a top concern of wildlife management agencies (Miller et al. 2008). Additionally there is concern for livestock safety (Hamir et al. 2007) and public health if strain adaptation allows infection of humans (Barria et al. 2011).

There is ample evidence that variation in the prion protein gene (PRNP) impacts host susceptibility to transmissible spongiform encephalopathies (TSEs). Research on human TSEs (Collinge et al. 1991) and scrapie (Tranulis 2002), as well as CWD (O'Rourke et al. 2007), has shown that PRNP variation influences the susceptibility to TSEs. Human prion diseases, such as Kuru, have been shown to drive strong balancing selection in exposed populations (Mead et al. 2003), and artificial selection for resistance has become an important measure in fighting prion diseases in livestock (Sweeney and Hanrahan 2008). Mechanisms for improved resistance include disruption of prion malformation reactions and reduced accumulation of abnormal prions (Caughey 2003). PRNP heterozygosities may be protective against prion disease progression if the conversion of normal cellular prion proteins to malformed prions is less efficient in hosts co-expressing different prion protein molecules (Caughey 2003).

Previous genetic research in Wisconsin identified two PRNP genotypes that could produce differential susceptibility to CWD in white-tailed deer (Johnson et al. 2006, Blanchong et al. 2009). A nucleotide substitution in the 96th codon leads to an amino acid change from glycine (Gly) to serine (Ser). White-tailed deer with at least one copy of the serine-coding allele may resist infection or delay the clinical stages of CWD compared to deer homozygous for glycine (referred to here as "96GG"). Gly-Gly homozygotes constituted 59.4% of our study population. Gly-Ser heterozygotes constituted 36.8% of the population, while Ser-Ser homozygotes constituted just 3.8% (these genotypes are jointly referred to as "96GS"). The 96GS genotype was detected in 44.4% of CWD-negative deer, vs. only 17.4% of CWD-positive deer sequences, showing strong evidence for disease resistance in this genotype (Johnson et al. 2006). The 96GS genotype has also been linked to slowed progression of CWD in infected deer (Johnson et al. 2006, Keane et al. 2008). In a deer farm sustaining unnaturally high CWD infection rates, Keane et al. (2008) found that the odds of infection were three times greater for 96GG compared to 96GS animals, and odds of advanced infection of the brain stem (obex) tissue were 12 times higher for 96GG animals. An additional nucleotide substitution in the 95th codon leads to an amino acid change from glutamine to histidine. Initial screening by Johnson and colleagues (2006) suggests strong potential for disease resistance in the Q95H genotype; however, because the histidine allele is rare (2% of deer), we were unable to evaluate its potential impact on CWD resistance.

Despite this general information that PRNP genotypes can influence CWD infection, little is known about how these genetic differences influence natural selection within cervid populations or how genetic makeup shapes the disease processes and population response to CWD. The suspected differences in infection and CWD progression rates provide reason to hypothesize that variation in PRNP genotypes confers a fitness advantage for free-ranging white-tailed deer, possibly leading to natural selection favoring resistant genotypes in CWD-affected populations. Potential genetic resistance may also be of interest for selective breeding to augment herd resistance (Cross and Burmester 2002). The goal of our research was to evaluate the importance of the 96GS genotype in shaping CWD transmission and disease morality, and to determine the potential fitness impacts of this genotype in the Wisconsin white-tailed deer population.

We used extensive genetic testing combined with epidemiological and population dynamic modeling to quantify the genotype-specific rates of CWD infection and related mortality and to predict the potential evolutionary impacts of CWD on a white-tailed deer population. We used an age–prevalence disease hazard model (described by Heisey et al. 2006) to estimate genotype-specific rates of CWD infection and disease-related mortality. These epidemiological rates were used in a population dynamics model to evaluate the potential impact that genotypic differences have on growth rates and genetic composition of the Wisconsin white-tailed deer population. These genetic differences in disease dynamics have not been previously documented, accounted for in management planning, or considered in current CWD models. Our research demonstrates the potential link between CWD and evolutionary processes in deer populations with direct

bearing on the epidemiology, dynamics, and future trends in CWD transmission and spread. We offer an innovative example of potential disease-driven selection by combining genetics and epidemiological modeling for a free-ranging wildlife population, in which we quantify the response of a specific gene to a specific pathogen.

Material and Methods

Study area and sampling

Our research was conducted within the core CWD outbreak area of south-central Wisconsin, where the disease pressure was highest (Joly et al. 2006, Osnas et al. 2009). Although first detected in 2002, CWD probably was established in this area more than 20 years ago (Wasserberg et al. 2009) Rates of CWD prevalence in the core have remained relatively constant since discovery, indicating generally consistent disease pressure on the study population (during the sampling period, average crude adult prevalence was 4.6% across the area, up to 16% in some sections; average prevalence among adult females was 3.9%) (Osnas et al. 2009).

We acquired lymph node tissue samples from harvested female deer sampled by the Wisconsin Department of Natural Resources (DNR) for routine CWD surveillance from 2002 to 2009. Sample location of each deer was recorded according to the 2.6-km^2 land section where it was reported harvested. Deer age was determined by trained DNR personnel according to tooth wear and replacement (Severinghaus 1949). Samples were tested for CWD via immunohistochemistry and/or plate ELISA (enzyme-linked immunosorbent assay) at the Wisconsin Veterinary Diagnostic Laboratory or the Illinois Department of Agriculture Diagnostic Laboratory (Keane et al. 2008).

We used age–prevalence data to estimate epidemiological parameters, including infection and disease-related mortality rates. Age-specific prevalence provides an efficient alternative to data gathered from long-term cohort studies (Keiding 1991). We sampled only female deer because heavy hunting pressure on male deer results in a younger age distribution, making it difficult to detect age-specific patterns and less likely that males experience CWD-related mortality before harvest (Storm 2011). We sampled all available infected females from the core area ($n = 44$ one-year-olds, 61 two-year-olds, 43 three-year-olds, 30 4–5-year-olds, and 14 6–8-year-olds). Samples were abundant for CWD-negative deer, so we selected a stratified random subsample within each age class, except in the oldest age class from which we took all available samples ($n = 188$ fawns, 166 one-year-olds, 171 two-year-olds, 138 three-year-olds, 176 4–5-year-olds, 88 6–8-year-olds). The proportions of 96GS and 96GG genotypes in each of the age, sex, and disease classes of our sample data were used to extrapolate PRNP genotype frequencies for the entire population of deer tested within each age and disease status group. We examined trends in PRNP genotype frequencies to determine differences in survival and epidemiological parameters.

PRNP genetic analysis

To efficiently determine the PRNP genotype, we developed a single nucleotide polymorphism (SNP) assay for rapid and cost-effective genotyping of the polymorphism of interest at codon 96 (based on previously published sequence with Genbank accession number AY330343; Raymond et al. 2000). Reactions were performed at the University of Wisconsin Biotechnology Center. Primer sequences were as follows:

AF156185-316_ALA
GAAGGTGACCAAGTTCATGCTGTGGTGGAG
GCTGGGGTCAAA

AF156185-316_ALG
GAAGGTCGGAGTCAACGGATTGGTGGAGG
CTGGGGTCAAG

AF156185-316_C1
CCTGCCACATGCTTCATGTTGGTTT.

Reactions were performed in 4-μL volumes consisting of 1 ng of DNA, 2 μL 2× Reaction Mix (KBioscience, Hoddesdon, UK), 400 μmol/L $MgCl_2$, and 0.055 μL Assay Mix [12 μmol/L primer AF156185-316_ALA, 12 μmol/L primer AF156185-316_ALG, 30 μmol/L primer AF156185-316_C1]. Initial denaturation was performed at 94°C for 15 min, followed by 20 cycles of 94°C for 20 s, 59°C for 5 s, 72°C for 10 s, then another 25 cycles of 94°C for 10 s, 59°C for 20 s, and 72°C for 40 s. After amplification, genotypes were read on a Biotek Synergy II plate reader (Biotek, Winooska, Vermont, USA) and were scored using the Bioconductor statistical package for R (*available online*).[7] In addition, over 450 samples from the core area were fully sequenced by Johnson et al. (2006) and we used DNA from 93 of these deer as a validation set to ensure reliable results from our SNP assay. We achieved a 100% match between SNP and full-sequence genotypes. For additional quality assurance measures (data not shown), we used microsatellite data to ensure that results could not be confounded by shifts in population structure between age groups (based on 776 samples genotyped by colleagues; Grear et al. 2010). We further used a Moran's I test to verify that patterns of PRNP genotypes were not confounded by spatial structure: $I = -0.0093$, $P = 0.96$ (performed in Geoda v0.9.5-i; Anselin et al. 2005).

Epidemiological modeling

We used an age–prevalence epidemiological model to determine the genotype-specific force of infection (λ_{GG}, λ_{GS}) and disease-induced mortality (μ_{GG}, μ_{GS}) rates that fit the changing patterns of CWD prevalence and allele frequency over age (surrogate for time). This age–prevalence model simultaneously accounts for accumu-

[7] http://www.bioconductor.org/

lation of infection with age and extra mortality (in addition to other causes of mortality) associated with becoming infected (Heisey et al. 2006). Our model assumed that the hazard rates for infection or mortality were constant, but that probability of becoming infected accumulated with exposure time (age) and probability of mortality increased with time since infection (Caley and Hone 2002). We fit a series of nested models to evaluate the importance of the infection and mortality parameters for each genotype based on the general epidemiological model for force of infection (λ), disease-induced mortality (μ), and age (t):

$$\text{prev}_t = \frac{1 - \exp[-(\lambda - \mu)t]}{1 - \left(\frac{\lambda}{\mu}\right)\exp[-(\lambda - \mu)t]}. \quad (1)$$

Although epidemiological parameters can be particularly difficult to estimate in free-living populations (McCallum et al. 2001), we used a hierarchical Bayesian approach (Cressie et al. 2009) to estimate genotype-specific epidemiological rates and incorporate prior information from laboratory studies on genotype-specific CWD-survival rates (solved in WinBUGS version 1.4.3; Imperial College and Medical Research Council, UK; code is available in the Supplement). We used informed priors for μ's according to the distribution of survival rates observed in a study of experimentally infected captive white-tailed deer: 96GG survived an 693.4 ± 30.4 d (mean ± SE); 96GS survived 955.7 ± 131.5 d (Johnson et al. 2011). We also estimated the model parameters using uninformative priors for λ's and μ's (uniformly distributed between 0 and 1) for comparison.

Because population-level genotype frequencies for the model were estimated from our sample, we employed multiple imputation to accommodate variation from projecting sampled genotype frequencies onto the larger study population. First, we assumed that the observed genotype proportion was represented by the mean of a beta distribution (for each age class in each infection class). Then, we recalculated the model over each of 10 new data sets generated by random draws from this beta distribution. We summarized the mean parameter estimates and full range of variation according to rules for combining multiple data sets (Rubin 1987).

Population model and selection projections

Theoretical research suggests that disease impacts can influence population growth and fitness as well as genetic composition and diversity (Anderson and May 1979). We therefore evaluated the potential fitness implications of differential genetic resistance to CWD. We used separate genotype-specific multi-state Leslie matrix models (Caswell 2001) with genotype-specific disease parameters and annual demographic rates for our study population. The baseline population matrix was constructed with previously published population survival and fecundity rates without harvest or disease mortality (Wasserberg et al. 2009). Then for each genotype, survival rates of CWD-negative deer were decreased by the genotype-specific annual probability of infection, and survival rates of CWD-positive deer were reduced by the annual disease-induced mortality rate. The dominant eigenvalue of the Leslie matrix represents the potential annual growth rate (R) of the population.

We used population growth rates to provide a biologically meaningful measure of fitness. We compared growth rates between uninfected populations and infected populations for each genotype. We calculated the relative fitness of the susceptible genotype compared to the resistant genotype (R_{GG}/R_{GS}); and the selection coefficient favoring resistance was then simply $1 - (R_{GG}/R_{GS})$ (Hartl and Clark 1997).

We used variations of the population matrix to evaluate the strength of selection under different potential scenarios. First, to ensure that our projections were not biased by prior information on disease mortality rates, we ran the population matrix using the simplest supported model ($\lambda_{GG\neq GS}$ $\mu_{GG=GS}$) with uniformed priors as well as the full genotype-specific model ($\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$) incorporating the informative Bayesian priors. In addition, we evaluated infection rates that might be typical of a heavily infected captive deer population. Cervid farms create an artificial concentration of deer in which social structure and behavioral interactions and/or environmental contamination may be altered in such a way as to create the opportunity for extremely high disease transmission (Miller and Wild 2004, Keane et al. 2008). One white-tailed deer farm in Wisconsin was depopulated after discovery of CWD infection; post mortem testing revealed both extremely high infection rates and genotype-specific infection rates (prevalence reached 88% in 96GG deer and 67% in 96GS deer; Keane et al. 2008). We ran population projections using infection rates from this farm to evaluate the effect that high disease pressure might have on selection.

Results

PRNP genetic analysis

The survival advantage of the CWD-resistant genotype was evident viewing age-specific trends in PRNP genotype frequency. The frequency of the 96GS genotype in CWD-negative deer increased with age (from 40.4% to 54.5%; Fig. 1), indicating differential rates of infection and/or disease mortality between genotypes. The odds of a CWD-negative female deer ($n = 927$) having at least one copy of the CWD-resistant 96GS allele increased by 1.1 times with each year of age ($P = 0.014$, from logistic regression). In CWD-infected animals ($n = 195$) the rate of increase was similar, although variation was greater. CWD prevalence accumulated more rapidly and achieved much higher levels in the 96GG genotype (up to 9.41% vs. 2.31% in 96GS; Fig. 2).

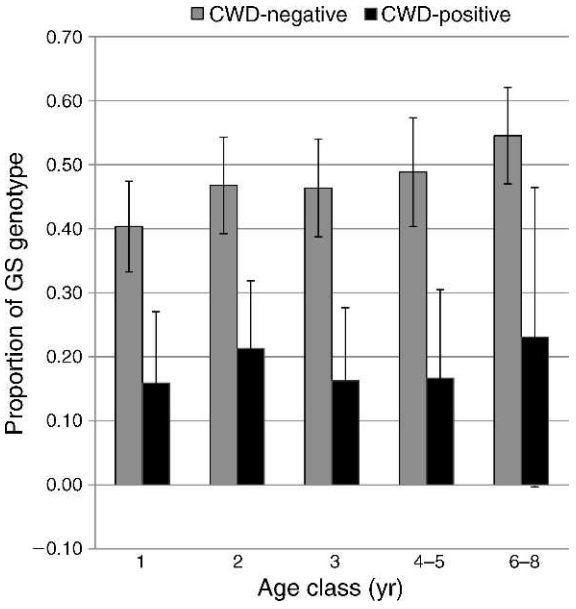

FIG. 1. Frequency of the GS genotype, which is resistant to chronic wasting disease (CWD), increases as female white-tailed deer age, as determined by PRNP single-nucleotide polymorphism (SNP) typing of CWD-negative and CWD-positive female deer sampled from the core CWD-infected area of Wisconsin, USA, during 2002–2009. Error bars represent 95% confidence intervals of the estimated sample proportions.

Epidemiological modeling

Through epidemiological modeling we demonstrated that genotypic differences in infection rate and disease-induced mortality shaped the patterns of CWD prevalence and allele frequency. Based on deviance information (DIC) scores, significant parameter estimates, and biological justification, the best epidemiological model was the full $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model incorporating prior experimental mortality data (Table 1). Posterior distributions of parameter estimates from the best models ($\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ followed by $\lambda_{GG\neq GS}$ $\mu_{GG=GS}$) had credible intervals indicating significant effects, and posterior distributions of parameters were symmetrical around the mean, with positive pD values (Table 1) indicating that DIC scores should be reliable (as discussed in Gelman et al. 2004). Models with no disease mortality ($\mu = 0$) were poorly supported by the data (Table 1; $\Delta DIC > 10.0$) and are contradicted by the previous biological knowledge that CWD is always fatal (Williams 2005). Models using a single infection rate parameter ($\lambda_{GG=GS}$) to fit both PRNP genotypes were also a poor fit to the data ($\Delta DIC > 52.0$), indicating strong trends in genotype-specific force of infection and CWD prevalence. However, models accounting for genotype-specific force of infection ($\lambda_{GG\neq GS}$ $\mu_{GG=GS}$ and $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$) performed similarly (Table 1; see fit in Fig. 2). To select among these two top models, we also relied on prior biological knowledge and quality of the parameter estimates. Posterior parameter distributions indicated that the model with noninformative priors was unable to estimate genotype-specific μ's (the posterior μ_{GS} distribution exceeded the maximum range; graph not shown, but see credible intervals in Table 1) and provided a wide confidence bounds for the difference between mortality rates ($\Delta\mu = -0.163$ (-0.710 to 0.462)) for the $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model without prior information. However, the $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model with informed priors gave a 99.02% posterior probability that $\Delta\mu$ was greater than zero ($\Delta\mu = 0.0318$ (0.0245–0.0395).

The $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model showed that annual CWD-infection rates were four times (95% CI 2.43–9.80) higher in the 96GG genotype ($\lambda_{GG} = 0.041$ (0.034–0.049), $\lambda_{GS} = 0.010$ (0.005–0.014)). When infected, animals with the 96GS genotype survived 48.9% (8.2 months) longer than the 96GG (mean survival based on μ ($\mu_{GG} = 0.493$ (0.431–0.555) = 16.9 (15.0–19.3) months for 96GG vs. $\mu_{GS} = 0.331$ (0.217–0.444) = 25.1 (18.7–25.1) months for 96GS). Our modeling confirms that each genotype experiences different CWD dynamics.

Population model and selection projections

When accounting for CWD impacts, population growth rates varied according to the disease susceptibility for each genotype. The dominant eigenvalue of each matrix showed that the average annual growth rate (R) of an unharvested 96GS population (1.354) was higher than an unharvested 96GG population (1.341) (based on

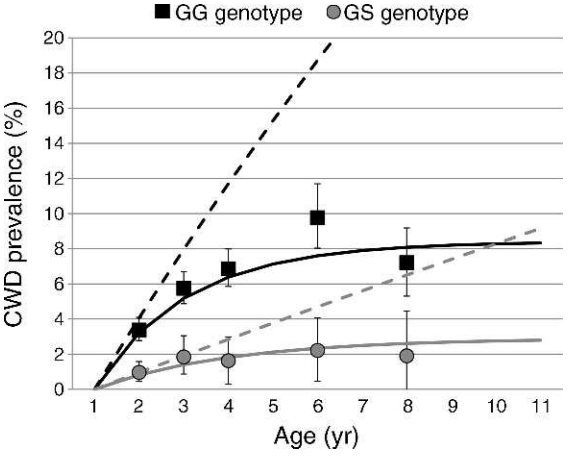

FIG. 2. CWD prevalence accumulates with age at PRNP genotype-specific rates. Symbols show the observed CWD prevalence in 96GG and 96GS genotypes for each age class of female deer within the core CWD-infected area of Wisconsin, USA. Error bars represent 95% credible intervals for population-level CWD prevalence estimated from 1000 binomial randomizations based observed allele frequencies and disease status. The curves in the graph show the estimated accumulation of CWD prevalence as animals age, predicted from competing epidemiological models. Solid lines represent the best model: $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ (black for GG, gray for GS). Dashed lines offer a comparison to the model with genotype-specific infection rates but no disease-induced mortality: $\lambda_{GG\neq GS}$ (black for GG, gray for GS).

TABLE 1. Comparison of alternative epidemiological models of chronic wasting disease (CWD) in white-tailed deer in Wisconsin, USA.

Candidate models	pD	DIC	ΔDIC	λ_{GG}	λ_{GS}	μ_{GG}	μ_{GS}
Informative priors on mortality							
$\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$	**2.024**	**54.036**	**0.057**	**0.041 (0.034–0.049)**	**0.010 (0.005–0.014)**	**0.493 (0.431–0.555)**	**0.331 (0.217–0.444)**
$\lambda_{GG\neq GS}$ $\mu_{GG=GS}$	2.001	53.979	0.000	0.042 (0.035–0.048)	0.012 (0.008–0.015)	0.493 (0.431–0.554)	= μGG
$\lambda_{GG\neq GS}$	1.966	64.019	10.040	0.021 (0.018–0.024)	0.006 (0.004– 0.007)	0.000	0.000
$\lambda_{GG=GS}$ $\mu_{GG\neq GS}$	1.296	106.695	52.716	0.027 (0.023–0.032)	na	0.437 (0.378–0.497)	0.534 (0.434–0.634)
$\lambda_{GG=GS}$ $\mu_{GG=GS}$	1.015	118.214	64.235	0.028 (0.024–0.032)	na	0.494 (0.433–0.555)	= μGG
$\lambda_{GG=GS}$	0.96	133.137	79.158	0.014 (0.012–0.016)	na	0.000	0.000
Noninformative priors							
$\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$	3.053	55.086	0.482	0.037 (0.020–0.055)	0.014 (0.006–0.022)	0.425 (0.054–0.797)	0.590 (0.098–1.082)
$\lambda_{GG\neq GS}$ $\mu_{GG=GS}$	**2.742**	**54.604**	**0.000**	**0.041 (0.034–0.049)**	**0.012 (0.007–0.017)**	**0.493 (0.431–0.554)**	= μGG
$\lambda_{GG\neq GS}$	1.963	64.257	9.653	0.020 (0.017–0.023)	0.006 (0.004–0.008)	0.000	0.000
$\lambda_{GG=GS}$ $\mu_{GG\neq GS}$	1.974	59.013	4.409	0.023 (0.018–0.029)	na	0.134 (−0.008 to 0.276)	0.905 (0.741–1.068)
$\lambda_{GG=GS}$ $\mu_{GG=GS}$	1.773	109.715	55.111	0.028 (0.016–0.040)	na	0.496 (0.141– 0.850)	= μGG
$\lambda_{GG=GS}$	0.986	123.113	68.509	0.014 (0.012–0.016)	na	0.000	0.000

Notes: Shown are parameter estimates for λ (force of infection) and μ (disease-induced mortality) with 95% Bayes credible intervals (CI) in parentheses, used to describe genotype-specific (GG, GS) disease dynamics of CWD. The selected models (in boldface) were rerun using multiple imputation to determine confidence bounds that accounted for variation in population estimates from sampling error. Abbreviations: pD is the posterior deviance for model parameters; DIC is the deviance information criterion; ΔDIC is change in DIC relative to the best model (lowest score); GG indicates animals with two copies of the allele coding for glycine at the 96th amino acid position in the PRNP gene; GS indicates animals with at least one copy of the allele coding for serine at the 96th amino acid position in the PRNP gene; GG=GS indicates models for which a single parameter is estimated referring to both genotypes; GG≠GS indicates models for which separated parameters are estimated for each genotype; "na" means not applicable.

the $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model; Table 2). The difference in population growth rates translated directly into a fitness advantage sufficient to drive selection favoring CWD-resistance in the infected population. The fitness advantage for CWD resistance led to an estimated selection coefficient of 0.0103, suggesting an increase in the 96GS genotype at a rate of >1%. This disease-driven selective pressure indicates the resistant serine allele could become dominant in the population within a few hundred years (Fig. 3; note that this graph shows the accumulation of the S allele over time, not the diploid 96GS genotype). Although the relative fitness advantage and selection coefficient favoring the 96GS PRNP type were smaller for the $\lambda_{GG\neq GS}$ $\mu_{GG=GS}$ model, the differences in genotype-specific force of infection were significant in both the $\lambda_{GG\neq GS}$ $\mu_{GG=GS}$ and $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ models (see Table 1), and these differences gave 96GS deer a substantial selection advantage over the 96GG type (Table 2). Although the $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ was the most biologically plausible model, conclusions of disease-driven selection were robust to alternate epidemiological models. Changes in the level of disease pressure, on the other hand, had substantial effects on the intensity of disease-driven selection. In our scenario for highly infected farmed cervids, the model produced a higher selection coefficient (up to 7.4%, based on the $\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$ model) and led to rapid dominance of resistant genotypes (Fig. 3).

DISCUSSION

Our study of CWD-affected white-tailed deer in Wisconsin provides an important link between wildlife population dynamics, epidemiology, and natural selection. Through genotyping and multilevel modeling we were able to quantify epidemiological and fitness

TABLE 2. PRNP (prion protein gene) genotype-specific population growth rates and selection coefficients.

Model R	Baseline R	R_{GG}	R_{GS}	Selection coefficient
No disease	1.357			na
$\lambda_{GG\neq GS}$ $\mu_{GG\neq GS}$		1.34	1.354	0.0103
$\lambda_{GG\neq GS}$ $\mu_{GG=GS}$		1.342	1.353	0.0083

Notes: Selection coefficients favor the 96GS PRNP genotype in white-tailed deer in Wisconsin, USA. Growth rates (dominant eigenvalues, denoted R) are shown for a Leslie-matrix population model using demographic rates from previous research without disease-adjusted survival parameters, and with survival adjusted for selected epidemiological models.

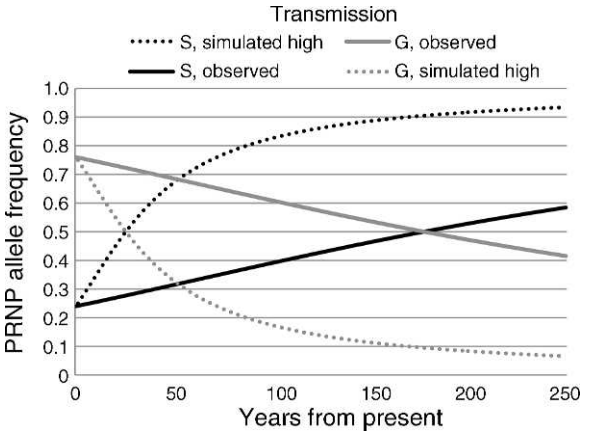

FIG. 3. Projected changes in PRNP allele frequency under selective pressure from CWD. The temporal trend in allele frequency is based on the selection coefficient favoring the serine allele (S) over the glycine allele (G), fitness differentials calculated from population matrix models parameterized with estimated genotype-specific disease infection and mortality rates. Time 0 represents the allele frequencies observed in our sample (note that this graph is based on allele frequencies, not diploid genotype frequencies). The solid lines are based on CWD transmission in the free-ranging deer population in the CWD-infected area of Wisconsin, USA. The dotted lines are based on extreme transmission values observed in a heavily infected captive deer farm (after Keane et al. 2008).

parameters, and evaluate the potential selective force of disease to an extent that is seldom possible in free-ranging wildlife populations. Our large genotyped sample and use of prior information in the Bayesian framework helped us to quantify the degree of CWD resistance in the 96GS genotype for both infection and mortality rates. We used a large age-stratified sample to evaluate population trends in CWD infection and survival. Prior information on disease mortality from captive deer research was also essential in estimating disease-induced mortality.

We assumed that deer of each genotype shared similar rates of background mortality, reproduction, and other fitness traits, and varied only in their survival rates as a result of susceptibility to CWD infection and/or CWD-induced mortality. Previous research in the Wisconsin CWD zone has indicated that deer experience the same harvest-related mortality pressure regardless of CWD status (Grear et al. 2006). To date, no research has addressed possible non-disease-related fitness differences in deer according to PRNP genotype. However, there is scant evidence suggesting that the PRNP gene would be under selective pressure for reasons not related to disease. Scrapie-resistance breeding programs for sheep in the European Union have examined fitness parameters associated with the PRNP genotype and found no evidence of negative association between TSE-resistant genotypes and reproduction or performance traits (Sweeney and Hanrahan 2008). However, one study suggested higher mortality rates in scrapie-resistant lambs (Sawalha et al. 2010). To be conservative, we used our population model to evaluate potential deviations from our assumption of similar baseline fawn survival rates between genotypes. We found that CWD selection would still favor the S allele unless SS fawns experienced mortality >2.3 times higher than 96GG fawns, and 96GS fawns experience mortality >1.5 times that of 96GG fawns (results not shown). This indicates that our conclusions of disease-driven selection are probably robust, even to strong deviations from the assumed baseline among genotypes. This topic merits further research in wild deer populations.

Our analysis indicates that the Wisconsin deer population is currently experiencing selective pressure exerted by CWD infection. The level of selection estimated for the CWD-resistant PRNP genotype was comparable to rates observed in human MHC genes known to affect immune response (Satta et al. 1994). Our results indicate the potential for rapid genotypic evolution in the white-tailed deer population (Fig. 3). However, we emphasize that the future trajectory is likely to be confounded by many complex ecological factors. For example, higher infection rates can elevate the selective advantage of the 96GS genotype. In contrast, frequent deer migration from a less infected area could dampen the effects of selection (Allendorf and Luikart 2007, Angers et al. 2010). High harvests in Wisconsin greatly increase deer mortality, irrespective of genotypic or disease status, which would dampen the selection advantage of CWD-resistance (Allendorf et al. 2008). Further, in projecting a constant selective pressure into the future, we assume no change in the disease agent. Although there is currently no evidence of distinct strain dynamics for CWD in deer (Angers et al. 2010), based on other prion disease systems we can infer that new strains or adaptations in prion infectivity could alter disease resistance and the selective advantage (Gonzalez et al. 2002).

Another unknown is whether the disease-driven selection may exert different pressures on the sexes. We did not evaluate PRNP patterns in males, because they experience much higher harvest mortality than females (Wasserberg et al. 2009) and few males live beyond the 4.5-year-old age group. Because males face strong harvest mortality pressure, which is unrelated to PRNP genotype, fewer male deer are likely to survive harvest long enough to die from CWD; therefore, we expect the survival advantage conferred by CWD resistance will be less important to male fitness. On the other hand, males experience CWD infection rates nearly twice those of females (Grear et al. 2006), which could increase the fitness benefit of CWD resistance. It seems likely that the elevated infection rates in males are related to social and behavioral differences between males and females, rather than inherent differences in disease susceptibility (Miller and Wild 2004, Miller and Conner 2005, Grear et al. 2006), so we would not expect the mechanisms of disease-driven selection to operate

differently in males than as we observed in females. Still, it is unclear how the greater infection pressure and harvest mortality might influence the selective forces acting on male deer; further research, perhaps including long-term tracking of male deer, is needed to determine the fitness impact.

Even under the relatively strong selective pressure that we observed, wild cervid populations are unlikely to evolve quickly enough for selection to influence disease management, although long-term selective breeding may be feasible for captive cervids (Dawson et al. 1998, Cross and Burmester 2002). Even low susceptibility (lower infection and higher survival) of the resistant genotype is likely to maintain endemic levels of disease that depend on the underlying rate of infection. Although relying on genetic change may not be viable for short-term disease management, CWD could exert considerable force to drive genetic evolution of host populations on an ecologically relevant timescale, especially in unharvested populations where greater CWD prevalence and mortality risk may lead to stronger selective pressure.

The discovery of disease-driven selection in the deer population raises additional questions for future research in both management and epidemiology. Managers know that selective harvest can impact the age and social structure of ungulate populations (Milner et al. 2007) and even nonselective harvest can have demographic effects that influence selection (Allendorf et al. 2008). It is unclear whether targeting certain age and sex classes might facilitate or impede the rate of selection for CWD resistance. For example, because the resistant 96GS genotype accumulates in older age classes, could harvest regulations targeting specific age classes speed the shift toward a 96GS-dominated population? Perhaps an even more pressing issue is to assess the costs and benefits of a 96GS-dominated deer population on CWD dynamics. It is unclear whether the lower infection rate of 96GS deer might be counteracted by their potential to live longer, and shed prions longer, once infected. An important future step in CWD research would be to examine the genotype-specific prion shedding rates throughout the course of disease and to better understand the importance of environmental transmission on disease dynamics.

Our study adds to the list of examples where heterogeneity in disease processes can be critical to understanding disease dynamics, potential population impacts, conservation of biological diversity, management strategies, and evolution. On a landscape scale, habitat characteristics and host community structure can influence parasite and disease dynamics (Ostfeld et al. 1995). At a finer scale, social organization and behavior can also determine contact rates and influence disease transmission (Altizer et al. 2003*b*, Cross et al. 2008, Grear et al. 2010). We extend these concepts to the importance of molecular heterogeneity in determining disease infection and mortality processes in wildlife populations.

Accounting for this genetic variation in CWD infection and mortality may improve epidemiological models. Current disease models suggest that twofold sex-based differences in CWD infection are important to disease dynamics and management (Grear et al. 2006). Further accounting for genetic heterogeneity in infection and mortality rates is likely to improve our understanding and prediction of CWD dynamics, spread, and environmental accumulation. We also note that failure to account for interindividual variations when modeling infection and mortality hazards can produce a shared frailty effect where individuals with the highest hazard are infected (and potentially die) first (Therneau and Grambsch 2000). Whether shared frailty due to genotypic differences is a potential factor in the apparent infection hazard rate decline reported for deer in our study area (Heisey et al. 2010) remains to be determined.

Considerable attention has been devoted to the direct impacts of infectious disease on biodiversity (Daszak et al. 2000) because disease can limit the abundance and distribution of species (van Riper et al. 1986) or contribute to decline or extinction of small populations (Schloegel et al. 2006). Our research demonstrates the more subtle effects of disease in shaping biodiversity at the fundamental level of genetic variation. We provide a unique empirical example of the potential for disease-driven selection to influence the evolution of a free-ranging host population; underscoring the importance of host genetic variation in the ability of populations to adapt to biological or environmental challenges.

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Supplemental Material

Supplement

Code for epidemiological model run in WinBUGS (*Ecological Archives* A022-058-S1).