**Introduction**

Chronic wasting disease (CWD) is a transmissible spongiform encephalopathy (TSE) that infects members of the Cervidae including elk (Cervus elaphus, Linnaeus, 1758), moose (Alces alces, Linnaeus, 1758), mule deer (Odocoileus hemionus hemionus, Rafinesque, 1817) and white-tailed deer (Odocoileus virginianus, Zimmermann, 1780) (Williams and Young 1980, 1982; Baeten et al. 2007). Infection occurs by transmission of a proteinaceous infectious particle (prion) (Prusiner 1998). TSE’s are always fatal and incubation is typically greater than one year before clinical signs develop, where the onset and duration of clinical signs vary (Williams and Young 1982; Williams et al. 2002). CWD is the only TSE to infect wild populations, and aside from scrapie is the only one that is infectious (Miller et al. 2000).

Chronic wasting disease has been detected in wild cervid populations in both the USA and Canada and continues to spread. Due to the potential long-term effects on economically important cervid populations (Williams et al. 2002; Bishop 2004; Joly et al. 2006), preventing further spread and eradication of the disease would be ideal (Conner et al. 2008). It is actively being managed in most areas but it is difficult to control due to the extended incubation period, the difficulty in detecting infectious individuals and the lack of vaccination or treatment (Williams et al. 2002; Joly et al. 2006; Sigurdson and Aguzzi 2007). Active management options are limited to enhanced surveillance, as well as selective and/or
nonselective culling (Williams et al. 2002). There is still much to learn about the long-term effects of CWD on wildlife and the affected ecosystems, but models indicate that CWD could lead to high mortality in mule deer populations where local extinctions may be necessary to eliminate the disease (Gross and Miller 2001).

The pattern of CWD spread is spatially heterogeneous and not a monotonic wave-front (Conner and Miller 2004; Miller and Conner 2005; Farnsworth et al. 2006), suggesting that numerous factors influence spread (Hastings et al. 2005). CWD transmission can occur directly, through the contact of infectious and susceptible individuals, or indirectly, through contact with infectious prions in the environment. Direct transmission is thought to be predominantly horizontal between interacting individuals, rather than vertical across the placental barrier (Miller and Williams 2003; Miller et al. 2006). Direct transmission is likely the predominate mechanism in a newly endemic region (Williams et al. 2002). Consequently, understanding the factors that influence horizontal transmission could lead to improved disease-control strategies.

Population genetics provides a potentially useful set of tools to study factors affecting disease spread if patterns of gene flow can be used as a proxy for the movement of infectious individuals. For instance, at the broad scale, a landscape genetic approach can identify genetic discontinuities among subpopulations that can be related to spatial and ecological factors that regulate gene flow (Manel et al. 2003; Holderegger and Wagner 2006; Storfer et al. 2007) resulting in the low risk of spread of disease. These low-risk regions can be targeted for disease control because intervention will be most effective here (Russell et al. 2005; Rees et al. 2008, 2009). Both Blanchong et al. (2008) and Cullingham et al. (2009) found rivers limited movement for the host (white-tailed deer and raccoons, respectively) population. These river barriers corresponded to reduced disease incidence, therefore defining regions where it would be possible to halt the spread of disease. At the local scale, transmission can be influenced by both social organization and the density of susceptible individuals (Altizer et al. 2003). Individual-based genetic analyses can be used to understand the social organization of individuals. As an example, white-tailed deer social structure tends to follow a matriarchic society (Hawkins and Klimstra 1970; Bowyer 1984; Mathews and Porter 1993; Aycrigg and Porter 1997; Skuldt et al. 2008), and maternal lineage has been shown to influence tuberculosis infection (Blanchong et al. 2006, 2007). Fine-scale genetics can indicate whether related individuals are spatially proximate, and at what distance this relationship decays (Hardy and Vekemans 1999).

Our aim was to assess broad (>1000 km) and local population genetic structure (<200 km) of male and female white-tailed deer across Alberta, Saskatchewan, and portions of British Columbia using bi-parentally inherited microsatellites and maternally inherited mitochondrial (mt) DNA to understand factors potentially influencing the broad-scale spatial spread and local transmission of CWD. At the broad-scale, we tested for isolation by distance (IBD) among sampling areas, where we expected higher levels of differentiation among females than males because males are the predominant dispersers (Hawkins and Klimstra 1970; Long et al. 2005; Nixon et al. 2007; Skuldt et al. 2008), and dispersal distances range from 7 km to over 50 km (Hawkins and Klimstra 1970; Rosenberry et al. 1999; Long et al. 2005; Skuldt et al. 2008). Additionally, deer dispersal can be influenced by habitat types and fragmentation (Long et al. 2005; Nixon et al. 2007; Skuldt et al. 2008), therefore we analyzed the genetic structure of white-tailed deer using a clustering algorithm (structure, Pritchard et al. 2000) to determine whether there was cryptic genetic structure across the landscape. At the local scale, we used an individual-based approach to elucidate factors influencing transmission among individuals. We used spatial-genetic autocorrelation to characterize patterns of relatedness among individuals within subpopulations where CWD is endemic, and related these patterns to the potential for disease transmission. Due to female philopatry, we expected to find significant relatedness among females at short distances, and no evidence of relatedness among males.

Methods

Study area and sample collection

The area sampled extends from eastern British Columbia to eastern Saskatchewan (longitude: −120 to −101, latitude: 49 to 59; Fig. 1) spanning rugged mountain terrain, parkland, boreal forest, and open prairie grasslands. A total of 2088 white-tailed deer (female = 1146, male = 837, unknown = 105) were selected for the analysis from samples collected by Alberta Fish and Wildlife, Saskatchewan Environment, British Columbia Ministry of the Environment, Canadian Cooperative Wildlife Health Centre, Parks Canada, and University of Saskatchewan. Tissue samples typically consisted of muscle biopsies or ear punches and were stored dry or in 95% ethanol at −20°C. Alberta samples (n = 1442) were collected from road-kill (~3%), government implemented hunter submissions (~41%), a CWD-targeted control program conducted from 2005 to 2008 (~56%), and Parks Canada (~1%). Most of the sampling by Alberta Fish and Wildlife occurred in the fall and winter when deer are more likely to associate in social groups (Geist 1998; Lingle 2003). Samples from Saskatchewan (n = 586) consisted of...
retropharyngeal lymph nodes from hunter surveillance (28%) and control program submissions (70%) and skin biopsies from anesthetized deer taken during research activities (2%) (2003–2007). Samples from British Columbia (n = 60) were collected from road kills and fall hunter submissions (~1%) as part of their CWD surveillance program. All samples were referenced by sex, age category (fawn, juvenile, adult), and geographic location (either GPS (n = 1444) or by wildlife management unit/zone (n = 644)). Age was determined by tooth eruption and wear for both Alberta hunter killed and Saskatchewan deer; AB winter program deer used both tooth information and body morphometrics. Centroids of wildlife management unit/zones were used for point locations where necessary. A total of 47 white-tailed deer (23 males and 24 females, of which 5 and 2 were juveniles, respectively) tested positive for CWD (Fig. 1).

Samples were grouped into subpopulations a priori for some of the broad-scale analyses. Subpopulations were based on management units and spatial clustering of

Figure 1 Distribution of 2088 white-tailed deer sample locations used for microsatellite analysis across the Canadian provinces of British Columbia, Alberta, and Saskatchewan. The shaded relief indicates the elevation and the location of the Rocky Mountains along the Alberta/British Columbia border. Subpopulation designations used in the mtDNA and microsatellite $F_{ST}$ analyses are indicated as polygons. All subpopulations were used for the microsatellite analysis, while subpopulations used for the mtDNA analysis are marked in white. Locations of chronic wasting disease positive cases in free-ranging white-tailed deer are indicated in red. The small insets below are the samples used in the fine-scale analyses. North border (NB) corresponds to the region demarcated at subpopulation 234AB, south border (SB) is 151AB, and Nipawin (NP) is 505SK.
DNA extraction and genetic profiling

DNA was extracted using Qiagen 96 DNeasy Blood and Tissue kit following the manufacturer’s protocol (Mississauga, ON, Canada). DNA was quantified using a NanoDrop 1000 (Thermo Fisher Scientific, Ottawa, ON, Canada) and diluted to 1 ng/µL for mt control region sequencing and 10 ng/µL for microsatellite analysis.

A representative subset (n = 557) including CWD-positive samples were selected for mtDNA control region sequencing. We aimed for a minimum of 10 individuals from subpopulations to provide broad coverage (Fig. 1). The control region was amplified using primers developed from published sequences (Miyamoto et al. 1990: accession ODOMTFVLA), forward primer – F1 (5’-TCT CCC TAA GAC TCA AGG AAG), and reverse primer – R1 (5’-GTC ATT AGT CCA TCG AGA TGT C). Reaction conditions were as follows: 2 ng template, 100 µm dNTPs, 15 nmol each primer, 1 U Invitrogen Taq (Burlington, ON, Canada) in a 1x PCR buffer [200 mm Tris–HCl (pH 8.4), 500 mm KCl] in a total volume of 20 µL. Polymerase chain reaction (PCR) cycles followed 94°C for 5 min, 30 cycles of 94°C for 30 s, 54°C for 30 s, and 72°C for 30 s, with a final extension of 2 min at 72°C; all amplifications were performed on Mastercycler ep gradient thermocyclers (Eppendorf). For fragment analysis, PCR products were diluted to 1:40 and analyzed on an ABI 3730 DNA Analyzer using GeneScan™ 500LIZ™ as a size standard (Applied Biosystems). Multiplex L1a and L1b were pooled for analysis on the ABI. Genotypes were scored manually using GeneMapper v4.0 software (Applied Biosystems).

To quantify error rates across loci, 95 duplicate samples were run and genotypes were compared. We identified potential inconsistencies and the presence of null alleles for the entire data set using micro-checker (Oosterhout et al. 2004).

mtDNA analyses

Sequences were trimmed and aligned manually in BioEdit (Hall 1999) and unique haplotypes were confirmed by sequencing in the reverse direction. Haplotype and nucleotide diversity measures were calculated in arlequin v3.11 (Excoffier et al. 2005). A mismatch distribution was examined for signatures of recent expansion (Rogers and Harpending 1992). Phylogenetic relationships among haplotypes were inferred using a median-joining network (Bandelt et al. 1999) produced using NETWORK version 4.5 (http://fluxus-engineering.com/sharenet.htm; accessed 5 February 2009). The network was generated using only haplotypes that occurred more than once for network clarity, transversions were weighted, and the value of epsilon was varied to ensure that the optimal tree was produced (Fluxus Technology Inc. 2008, Suffolk, England).

Diversity measures and genetic differentiation among subpopulations was estimated using arlequin v3.11 using both ΦST (Excoffier et al. 1992) and the traditional approach (FST), which only considers haplotype frequencies. We used a Mantel test (Mantel 1967) to test for IBD. Prior to Mantel testing, the geographic distance matrix was log-transformed and the genetic matrix was also transformed [FST/(1 – FST)] as recommended by Rousset (1997). All Mantel tests were carried out in zt-win (Bonnet and Van de Peer 2002) using 10 000 permutations.

Microsatellite analysis

Allelic diversity, observed (H0), and expected (He) heterozygosity were calculated in GenAlEx v6.1 (Peakall and Smouse 2006). GenePop (Raymond and Rousset 1995; web version, http://genepop.curtin.edu.au/) was used to test for Hardy–Weinberg equilibrium (HWE) and linkage disequilibrium (LD) using exact tests. All measures were calculated for the global data set and the subpopulations. The Bonferroni correction was applied to
correct for multiple statistical tests (Petit et al. 2001) to minimize Type I error (Zar 1999).

**Broad-scale population structure**

Analysis at the broad scale was conducted using two approaches. First, we assessed patterns of genetic differentiation among subpopulations using Mantel tests (Mantel 1967). This procedure tests for association between geographic and genetic distance matrices where a positive association indicates IBD. We also assessed IBD with respect to directionality by constraining the geographic distance matrix to east–west distance and north–south distance. We used two different measures of genetic differentiation, $F_{ST}$ and Jost’s (2008) $D$, because recent literature has indicated $F_{ST}$ does not accurately reflect genetic differentiation when heterozygosities within subpopulations are high (Jost 2008, 2009; Heller and Siegismund 2009). We compared females and males separately analyzing only subpopulations with $n > 20$ males and females combined. Geographic and $F_{ST}$ matrices were generated using spgdi1.2 (Hardy and Vekemans 2002). $D$ was calculated among subpopulations using the arithmetic mean across loci using smogd (Crawford 2009). Transformation of distance matrices and Mantel testing were conducted as described for the mtDNA analysis.

We also assessed population structure using microsatellites across the entire study area independent of subpopulation designation using the Bayesian clustering program STRUCTURE 2.2 (Pritchard et al. 2000; Falush et al. 2003, 2007). This program groups individuals into $K$ genetically homogenous population clusters that optimize HWE. We chose the conservative admixture model and ran five simulations at each $K$ (for $K = 1–6$) with a burn-in period of 100 000 Markov chains and 500 000 chains for data collection. The optimal $K$ was selected by analyzing the relative change in the Ln probability of the runs using the equation developed by Evanno et al. (2005), as well as a thorough inspection of the assignment probabilities of individuals. Other methods of cluster analysis were not considered [i.e. Geneland (Guillot et al. 2005) or TESS (Francois et al. 2006)] because Chen et al. (2007) found that they do not perform as well when genetic connectivity is high.

**Fine-scale population structure**

We looked at genetic spatial autocorrelation within three regions: Nipawin (NP; $n = 234, 1961 \text{ km}^2$), North Border (NB; $n = 498, 2142 \text{ km}^2$), and South Border (SB; $n = 354, 1652 \text{ km}^2$) (Fig. 1). These areas were selected because they have large numbers of geo-referenced samples and they are CWD-endemic regions. We used Moran’s $I$ statistic for genetic data (Legendre and Fortin 1989; Hardy and Vekemans 1999) to estimate relative relatedness among individuals at 500 m distance classes up to 3000 m. This was calculated separately in each region for each sex class in spgdi1.2 (Hardy and Vekemans 2002). Significance of the autocorrelation was assessed by permuting individuals and locations for each distance class 10 000 times. The significance of the correlogram was evaluated using the progressive Bonferroni adjustment (Legendre and Fortin 1989).

To determine whether disease status was associated with relatedness, we calculated pair-wise relatedness among positive CWD cases in NP and compared the distribution with pair-wise relatedness of matched, nondiseased ‘case–controls’, where we matched sex, location, and where possible age. We restricted our analysis to NP because it is the region with the greatest number of positive white-tailed deer cases. Pair-wise relatedness (Queller and Goodnight 1989) between individuals within groups was calculated in spgdi1.2 (Hardy and Vekemans 2002) using all samples from NP as the baseline. The distributions of pair-wise relatedness values are not independent points, so we used a nonparametric permutation approach to test for a significant difference between the means (Dietz 1983). In R version 2.9.1, we developed a script that generates two random samples from all of our pair-wise values (without replacement) and calculates the difference between the means. We permuted this 10 000 times to generate a distribution and compared with our actual value; if our value was within 95% of the distribution then our null hypothesis would be accepted.

**Results**

**mtDNA analyses**

Following sequence alignment and end trimming, we identified 79 variable sites comprising 37 haplotypes in a 611-bp fragment. The majority of sites were transitions (73); however, there were three transversions, two sites with both transitions and transversions, and one single base pair insertion. Haplotype diversity was $0.857 \pm 0.014$ and nucleotide diversity was $0.020 \pm 0.001$. The mismatch distribution was characterized by three peaks and did not indicate any signal of recent expansion. The resulting network indicates a number of lineages (Fig. 2) that are not spatially segregated (Fig. 3). We characterized haplotypes in 45 CWD-positive deer, and found similar haplotype diversity as in the total sample.

Samples from 10 subpopulations (Fig. 1, Table 1, $n = 8–240$) were sequenced. Subpopulation 112AB had relatively lower haplotype diversity ($H = 0.417$). Nucleotide diversity ranged from 0.003 to 0.023, where higher values indicated the presence of different lineages within...
that region. Global differentiation was low, $F_{ST} = 0.015$ ($P = 0.009$) and $\Phi_{ST} = 0.010$ ($P = 0.112$). Patterns of pair-wise genetic differentiation for $F_{ST}$ and $\Phi_{ST}$ were similar and mostly nonsignificant (35/45 and 37/45, respectively). Most of the significant comparisons involved British Columbia South (BCS), the only sample

**Figure 2** Median-joining network of 37 white-tailed deer haplotypes, haplotypes that occurred only once ($n = 14$) are not included for clarity. Circles are proportioned to represent the number of individuals sharing each haplotype and the colors correspond to the pie charts in Fig. 3 to indicate individual haplotypes.

**Figure 3** Pie charts indicate the distribution of white-tailed deer mtDNA haplotypes for each subpopulation in western Canada. The colors of the pie pieces correspond to Fig. 2 for reference.
to the west of the Rocky Mountains. Genetic and geographic distances were not correlated (Mantel tests: $F_{ST}$, $r = 0.09$, $P = 0.321$ and $F_{ST}$, $r = 0.15$, $P = 0.248$; Fig. 4). Due to higher pair-wise genetic differences between BCS and all other subpopulations, we performed a post hoc partial Mantel test using the separation of subpopulations across the Rocky Mountains. This separation explained 50% of the variance in $F_{ST}$ among subpopulations (partial Mantel test: $r = 0.71$, $P = 0.027$; Fig. 4).

Microsatellite analysis

Genetic profiles were generated for 2088 individuals with 1.9% missing data, and <1% error rate overall. The loci used were highly variable with the number of alleles/locus ranging from 6 to 27, with an overall observed heterozygosity of 0.677 (Table 2). Global $F_{IS}$ for each locus ranged from $-0.008$ to 0.140, and was statistically significant from 0 at six loci following Bonferroni correction. LD was significant in 4 of 91 pair-wise comparisons ($n$ with Rt5 and OCAM, INRA011 with OarFCB193, and OCAM with BM6438). These loci are unlikely to be linked because subpopulation LD analysis did not support the associations, and they have been considered independent in previous population-genetic studies on white-tailed deer (Dewoody et al. 1995; DeYoung et al. 2002; Jones et al. 2002). Observed heterozygosities were similar across subpopulations ($0.539$–$0.743$).

Figure 4 $\Phi_{ST}$ as a measure of genetic distance at the mtDNA control region plotted as a function of geographic distance between white-tailed deer subpopulations. Distances between subpopulations separated by the Rocky Mountains are indicated by black squares.

Broad-scale population structure

Global genetic differentiation was very weak but statistically significant ($F_{ST} = 0.006$, $P < 0.001$, $D = 0.022$) and genetic differentiation between subpopulations was positively related to their geographic distance (Mantel tests:...
may be two genetic clusters in the data. Large differences in sample size can affect the ability of STRUCTURE to detect all populations (Serre and Paabo 2004; Rosenberg et al. 2005). When we performed a post hoc analysis using a subset of samples (112AB, BCS, BNP, and Jasper) and the same initial model parameters, we found evidence of $K = 2$, with 87% of BCS samples assigned to cluster 1 with over 0.80 membership and 61% of the Alberta samples assigned to cluster 2.

**Fine-scale population structure**

Spatial genetic autocorrelation disappeared by 1000 m in female white-tailed deer in NP, NB, and SB (NP, $N_F = 173$; NB, $N_F = 277$; SB, $N_F = 215$; Fig. 6). Spatial autocorrelation among females at 500 m at NP ($I = 0.052$; Fig. 6) was much greater than among females separated by 500 m at NB ($I = 0.019$; Fig. 6) and SB ($I = 0.016$; Fig. 6). Males were unrelated at all distances at the NB and SB (NB, $N_M = 184$, SB, $N_M = 139$), and were not tested in NP due to low sample size ($N_M = 61$).

Distributions of relatedness among diseased and case–control deer in NP did not significantly differ based on our permutation test (diseased = $-0.020 \pm 0.008$, case–control = $-0.025 \pm 0.007$).

**Discussion**

White-tailed deer were very weakly differentiated by genetics within our study area indicating an overall absence of historical and current barriers to gene flow east of the Rocky Mountains. In the early to middle 1900s, white-tailed deer populations on the Canadian prairies expanded from extremely low levels both in
numbers and in the extent of their range (Wishart 1984; Natural Resources Service 1995). If their expansion occurred as a slow moving front, any signature of expansion would not be apparent and heterozygosity would have been maintained (Austerlitz et al. 1997). These expansion events together with the natural capability of deer to disperse distances of over 50 km (Hawkins and Klimstra 1970; Nelson 1993; Rosenberry et al. 1999; Long et al. 2005) likely lead to the weak population structure that we observed in both the mtDNA and microsatellite data. Previous genetic studies on white-tailed deer also show weak population structure (DeYoung et al. 2003; Doerner et al. 2005; Blanchong et al. 2008). The exception to this are populations in the south-eastern USA that show greater genetic differentiation (Ellsworth et al. 1994; Purdue et al. 2000), this is likely due to the stable history of these populations both pre- and post-Pleistocene (Cronin 1991; Purdue et al. 2000). Geographic distance does not explain genetic differentiation along the east/west axis but it does for the north/south axis. The absence of genetic differentiation along the east–west axis could result from dispersal along the major river drainages in the study area as they are oriented east-west (Fig. 1).

Mammalian dispersal is often sex-biased, where males disperse and females remain philopatric (Greenwood 1980; Handley and Perrin 2007). When female philopatry is strong, different patterns of genetic differentiation between males and females arise, and patterns measured by maternal and bi-parental genetic markers are likely to differ (Storz 1999; Goudet et al. 2002; Prugnolle and

Figure 6 Moran’s I among female and male white-tailed deer in the North Border (NB – top graphs), in the South Border (SB – middle graphs), and females in Nipawin (bottom graph). Open symbols indicate significant values >0 following a progressive Bonferroni correction. Jackknife estimates of standard error are shown.
de Meeus 2002; Avise 2004). Our fine-scale analyses support female philopatry at the local level, suggesting a larger proportion of females remain philopatric. However, we found weak mtDNA differentiation and similar levels of male and female microsatellite differentiation at broad scales, even though male white-tailed deer are the predominant dispersers (Hawkins and Klimstra 1970; Nelson and Mech 1984; Aycrigg and Porter 1997; Kilpatrick et al. 2001). There may be several reasons for this. First, due to recent range expansion across the Canadian Prairies, the populations may not be in mutation-drift equilibrium and therefore population structure has not had the time to establish (Ibrahim et al. 1996). Second, because deer have a high effective population size, a limited number of female dispersers would prevent the development of sex-biased differentiation (Mills and Allendorf 1996). Third, hunting can alter deer behavior (Williams et al. 2008) and affect genetic population structure (Allendorf et al. 2008).

The low overall genetic differentiation and absence of barriers to gene flow across Alberta and Saskatchewan suggest that CWD has the potential to spread from current foci of infection across the region over the long-term via dispersal. However, genetic structure across the Rocky Mountains implies a potential barrier to disease spread into British Columbia. At present, there are three major disease foci across Alberta and Saskatchewan, which are each separated by over 300 km. Each disease focus likely originated independently through contact between infected individuals in farming facilities and wild animals (Williams et al. 2002; Bollinger et al. 2004; Vercauteren et al. 2007). In the 13 years since CWD was first detected in captive cervids in Saskatchewan, documented cases of CWD remain highly clustered. Detection of CWD tends to be higher in males (Grear et al. 2006; Osnas et al. 2009) and a high proportion of white-tailed juvenile males disperse (46–80%; Hawkins and Klimstra 1970; Nelson and Mech 1984; Dusek et al. 1989; Nelson 1993; Nixon et al. 2007; Skuldt et al. 2008), therefore young male white-tailed deer may be the most likely vectors for long-distance disease spread in the short term. As a result, the distribution of male dispersal distances may be the most appropriate metric for estimating the per generation contribution risk, the difference in prevalence among the regions could be related to the degree of social cohesion. From this, we would expect to see increased relatedness among infected individuals, for example increased relatedness among deer has been found in white-tailed deer infected with bovine tuberculosis (Blanchong et al. 2007). However, we did not detect elevated relatedness among CWD-infected pairs of white-tailed deer, but our sample size was limited by the small number of positive cases. CWD prevalence is higher in mule deer than white-tailed deer in Alberta, where approximately 90% of cases are mule deer. Nakada (2009) surveyed mule deer spatial-genetic structure in both the NB and SB using most of
the same microsatellite loci reported here with samples collected under the same surveillance program and found higher levels of relatedness in both regions than we estimated for white-tailed deer (at 500 m: NB, $I_{MD} = 0.04$, $I_{WTD} = 0.02$; SB, $I_{MD} = 0.09$, $I_{WTD} = 0.01$) suggesting stronger social cohesion. In addition, diseased individuals were found to be more related than noninfected individuals. If there is elevated transmission within social groups of related deer, this would suggest that the pattern of spatial autocorrelation among female white-tailed deer may indicate the range of increased local transmission risk. Female pairs within <1000 m are positively related in all three regions. Although there are other factors that could also contribute to regional and species differences including disease sampling effort, time since CWD was established, density of deer, differential land-use, winter behavior, hunting pressure, and predation, they are beyond the scope of this analysis. It is also important to note that our study focused on deer-to-deer transmission. Environmentally mediated transmission is also likely to be important, since biological material such as saliva, urine, blood, feces, and carcasses are infectious (Miller and Williams 2003; Miller et al. 2004, Mathiason et al. 2006; Johnson et al. 2007; Haley et al. 2009; Tamgûney et al. 2009). However, the contribution of environmental contamination to disease spread is not known.

**Disease management**

Disease dynamics may occur at two spatial scales. At a broad-scale, biased dispersal can create opportunities for longer-distance disease spread. At a local scale, social cohesion and matriarchal associations provide a context for within-group transmission dynamics. Current CWD control programs are limited to density-reduction methods (Williams et al. 2002; Pybus and Hwang 2008) with the goal of reducing CWD prevalence or eliminating it from newly infected regions. The three main approaches to accomplish this are: (i) increasing hunter quotas, (ii) nonselective culling (Joly et al. 2006) and (iii) test and cull. For test and cull, testing is either conducted on live animals in the field that are removed once CWD infection is confirmed (Wolfe et al. 2004) or hunter submissions are tested and culls are carried out in the area where positive animals were harvested (Pybus 2007; Connor et al. 2007). Given our data, a combination of these approaches could contribute to reducing disease spread. Hunting seasons generally coincide with fall dispersal, and juvenile dispersing males are the most vulnerable to hunting mortality (Nelson and Mech 1986; Rosenberry et al. 1999; McCoy et al. 2005). By increasing hunter quotas for males, the number of successful male juvenile dispersers would be reduced, which could potentially limit the geographic spread of CWD (Gross and Miller 2001). Additionally the extent of surveillance should consider the migration patterns as these movements may provide alternative means of geographic spread. For test and cull strategies to be effective, the extent and timing of the cull must be considered. Because the factors that influence transmission are poorly understood (Gross and Miller 2001; Williams et al. 2002; Wasserberg et al. 2009), the culled regions have been calculated based on deer home-range size (7.25 and 3 km radii; Joly et al. 2006; Pybus 2007, respectively). For female–female interactions, the extent of the cull should include all individuals that potentially interacted with the diseased individual, i.e. the extent of positive spatial autocorrelation (<1000 m).

Wolfe et al. (2004) did not find the removal of CWD-positive animals to have an effect on overall disease incidence. However, they removed only the individual infected, where other members in their social group may have contracted the disease and should have been removed as well. Regarding timing, deer form their social groups during the fall and winter seasons (Lingle 2003), therefore culls should be conducted during these seasons to ensure that the individuals associated with the positive case are eliminated. Male–male and male–female interactions also likely play a role in disease transmission (Miller and Williams 2003; Joly et al. 2006; Wasserberg et al. 2009), therefore the extent and timing of these interactions will also need to be considered in management strategies.

Chronic wasting disease is relatively new, and hence there is still considerable uncertainty regarding transmission, resistance, and long-term persistence (Williams et al. 2002; Wasserberg et al. 2009). Future CWD research should focus on two areas, understanding factors associated with spread and transmission, and disease prevention. In terms of better understanding transmission and spread, we need to determine how migratory movements and different seasonal behaviors contribute to disease spread. We also need to estimate the risk of transmission from environmental contamination and understand how it contributes to persistence (Miller et al. 2004, 2006). For disease prevention, the development of prophylactic treatment such as a vaccine is important. Wildlife managers would be better equipped to manage and potentially eradicate the disease with these tools. The use of oral vaccination for other wildlife diseases such as rabies (Cross et al. 2007) has been effective.

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### Appendix: Microsatellite primer information

Locus information for 16 microsatellites used to amplify white-tailed deer, included are forward and reverse primer sequence, multiplex panel, primer concentrations, florescent label and source.

| Panel | Locus | Primer sequence | Primer (µ) | Label | Reference |
|-------|-------|-----------------|------------|-------|-----------|
| 1a    | BM6438| 5‘-TTGAGCACACACAGACAGCTGG | 0.30 | PET | Bishop et al. (1994) |
|       | N     | 5‘-TCCAGAAGAAACCAACTAG | 0.20 | NED | Jones et al. (2002) |
|       | O     | 5‘-AGGAGGAGCTGTTTCC | 0.20 | 6-FAM | Jones et al. (2002) |
|       | Cervid1 | 5‘-AACAGGACACACCGCC | 0.10 | VIC | Wilson and Strobeck (1999) |
|       | INRA011| 5‘-AGTTCGGAGATGTAGCACAC | 0.25 | PET | Dewoody et al. (1995) |
|       | OCAM  | 5‘-CTTCGTTTCTTCTCCAGTAC | 0.10 | NED | Vainman et al. (1992) |
|       | OCAM  | 5‘-AGGAGGACACACCGCC | 0.25 | VIC | Moore et al. (1992) |
| 1b    | BB12  | 5‘-GCTCTCTTGACGCTCCTTGT | 0.10 | VIC | Wilson and Strobeck (1999) |
|       | BL25  | 5‘-AACAGTGGGCAATGAGTGG | 0.10 | VIC | Bishop et al. (1994) |
|       | BM4107| 5‘-AGGAGGAGCTGTTTCC | 0.20 | PET | Bishop et al. (1994) |
|       | K     | 5‘-AGGGAGGAGAGAGGAGCACTA | 0.20 | PET | Jones et al. (2002) |
### Appendix: (Continued)

| Panel   | Locus               | Primer sequence                  | Primer (μM) | Label  | Reference                  |
|---------|---------------------|----------------------------------|-------------|--------|---------------------------|
| OarFCB193 | 5'-TTCTATCTAGACTGGGATTCAGAAAGGC 5'-GCTTGGAAATAACCTCTCTGCATCCC | 0.20          | 6-FAM     | Buchanan and Crawford (1993) |
| R       | 5'-GGGGTTCTCTCAATCCA 5'-TCAGTTGGAACCTCAAAGT | 0.20          | 6-FAM     | Jones et al. (2002)       |
| Rt5     | 5'-AATCCATGACAGGAG 5'-CAGCATAATCTGGACAGTG | 0.20          | VIC        | Wilson et al. (1997)      |
| Rt7     | 5'-CCTGTTCATCTCTCTCTCTC 5'-ACTTTCACGGGCACTGGTT | 0.20          | VIC        | Wilson et al. (1997)      |