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Avian oncogenesis induced by lymphoproliferative disease virus: A neglected or emerging retroviral pathogen?

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ABSTRACT

Lymphoproliferative disease virus (LPDV) is an exogenous oncogenic retrovirus that induces lymphoid tumors in some galliform species of birds. Historically, outbreaks of LPDV have been reported from Europe and Israel. Although the virus has previously never been detected in North America, herein we describe the widespread distribution, genetic diversity, pathogenesis, and evolution of LPDV in the United States. Characterization of the provirus genome of the index LPDV case from North America demonstrated an 88% nucleotide identity to the Israeli prototype strain. Although phylogenetic analysis indicated that the majority of viruses fell into a single North American lineage, a small subset of viruses from South Carolina were most closely related to the Israeli prototype. These results suggest that LPDV was transferred between continents to initiate outbreaks of disease. However, the direction (New World to Old World or vice versa), mechanism, and time frame of the transcontinental spread currently remain unknown.

Introduction

Lymphoproliferative disease virus (LPDV) is an exogenous retrovirus that induces a neoplastic syndrome in domestic turkeys (*Meleagris gallopavo*), resulting in the formation of lymphoid tumors in multiple organs (Biggs et al., 1978). Although there is circumstantial evidence of LPDV-like outbreaks occurring in domestic turkeys in Europe prior to the 1970s, the virus was not identified as an etiological agent of disease until 1972 in the United Kingdom (Biggs et al., 1974). Within a few years of its recognition, LPDV outbreaks were documented in additional European countries as well as Israel (Biggs, 1997; Ianconescu et al., 1983). These outbreaks remained confined to the European-Middle Eastern region and the virus has never been detected outside of this area, including North America. Although LPDV is characterized as an oncogenic retrovirus, it does not contain a putative viral oncogene, nor does it appear to exert its oncogenic effects through insertional mutagenesis of a cellular proto-oncogene; thus, the mechanism by which lymphoproliferative disease is induced is unknown (Chajut et al., 1991; Sarid et al., 1994; Gazit and Yaniv, 1999).

In domestic turkeys, disease due to LPDV infection is generally first noted around eight to 10 weeks of age, with a variable flock mortality that can reach 25% (Gazit and Yaniv, 1999; Biggs, 1997). The characteristic lesion of LPDV infection is a pleomorphic infiltrate of lymphocytes, including lymphoblasts intermixed with plasma cells and monocytic reticular cells in multiple tissues. The most commonly affected organs are spleen, thymus, pancreas, and liver, although smaller focal lesions can be present in a variety of other tissues (Biggs, 1997). LPDV has been demonstrated experimentally to infect both turkeys and chickens (*Gallus gallus*), although not ducks or geese (species not listed; Ianconescu et al.,

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Table 1
LPDV strains recovered in the United States from 2009 to 2012 that were analyzed during the study. LPDV-positive birds that were also positive for *reticuloendotheliosis virus* (REV) and/or *fowlpox virus* (FWPV) are indicated.

Virus[a]	County	State	Date	Collection method[b]	GenBank ID[c]	FWPV	REV
3/KS/2009	Logan	Kansas	2009	Diagnostic case	KC801949	×	×
12/AR/2009	Columbia	Arkansas	2009	Diagnostic case	KC802224	×	×
122/WV/2009	Randolph	West Virginia	2009	Diagnostic case	KC801950	×	×
286/WV/2009	Upshur	West Virginia	2009	Diagnostic case	KC801993	×	×
47/WV/2010	Upshur	West Virginia	2010	Diagnostic case	KC801994	×	×
183/WV/2010	Wayne	West Virginia	2010	Diagnostic case	KC801951	×	×
27h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC801981	*	*
28h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC802003	*	*
34h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC801982	*	*
35h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC801983	*	*
37h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC801984	*	*
38h/SC/2011	Barnwell	South Carolina	2011	Seasonal harvest	KC801985	*	*
48h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801986	*	*
52h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801987	*	*
54h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801988	*	*
59h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801989	*	*
61h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC802004	*	*
62h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801976	*	*
65h/SC/2011	Aiken	South Carolina	2011	Seasonal harvest	KC801990	*	*
67h/SC/2011	Dorchester	South Carolina	2011	Seasonal harvest	KC802005	*	*
68h/SC/2011	Dorchester	South Carolina	2011	Seasonal harvest	KC801975	*	*
69h/SC/2011	Dorchester	South Carolina	2011	Seasonal harvest	KC801991	*	*
70h/SC/2011	Dorchester	South Carolina	2011	Seasonal harvest	KC801992	*	*
90/WV/2011	Logan	West Virginia	2011	Diagnostic case	KC801995	*	×
152/GA/2011	Putnam	Georgia	2011	Diagnostic case	KC801952	×	×
141/CO/2012	Las Animas	Colorado	2012	Diagnostic case	KC801953	×	×
71/MO/2012	St. Clair	Missouri	2012	Diagnostic case	KC801954	×	×
95/WV/2012	Morgan	West Virginia	2012	Diagnostic case	KC801955	☑	☑
159/PA/2012	Clearfield	Pennsylvania	2012	Diagnostic case	KC801996	×	☑
163-A/NY/2012	Columbia	New York	2012	Diagnostic case	KC801997	×	☑
163-B/NY/2012	Columbia	New York	2012	Diagnostic case	KC801998	×	☑
165-A/ME/2012	Piscataquis	Maine	2012	Diagnostic case	KC801999	☑	☑
165-C/ME/2012	Piscataquis	Maine	2012	Diagnostic case	KC802000	×	×
169/MD/2012	Allegany	Maryland	2012	Diagnostic case	KC802001	*	☑
196/NC/2012	Bertie	North Carolina	2012	Diagnostic case	KC802002	×	☑
205/MO/2012	Howard	Missouri	2012	Diagnostic case	KC801956	*	×
216/PA/2012	Lackawanna	Pennsylvania	2012	Diagnostic case	KC801957	*	×
217/LA/2012	East Feliciana	Louisiana	2012	Diagnostic case	KC801958	*	×
453/NJ/2012	Sussex	New Jersey	2012	Diagnostic case	KC801959	×	☑
514/OH/2012	Hancock	Ohio	2012	Diagnostic case	KC801977	×	×
517-B/ME/2012	Cumberland	Maine	2012	Diagnostic case	KC801960	×	☑
535/PA/2012	Blair	Pennsylvania	2012	Diagnostic case	KC801961	☑	×
560/PA/2012	Huntingdon	Pennsylvania	2012	Diagnostic case	KC801962	☑	☑
592/MS/2012	Monroe	Mississippi	2012	Diagnostic case	KC801963	×	×
604-A/NH/2012	Concord	New Hampshire	2012	Diagnostic case	KC801964	☑	☑
604-B/NH/2012	Sutton	New Hampshire	2012	Diagnostic case	KC801965	☑	☑
604-C/NH/2012	Lisbon	New Hampshire	2012	Diagnostic case	KC801966	☑	☑
604-D/NH/2012	Bradford	New Hampshire	2012	Diagnostic case	KC801967	☑	☑
604-E/NH/2012	Hinsdale	New Hampshire	2012	Diagnostic case	KC801968	☑	☑
604-F/NH/2012	Dublin	New Hampshire	2012	Diagnostic case	KC801969	☑	☑
621/NC/2012	Hertford	North Carolina	2012	Diagnostic case	KC801978	☑	×
640/IN/2012	Orange	Indiana	2012	Diagnostic case	KC801979	*	×
648/WV/2012	Braxton	West Virginia	2012	Diagnostic case	KC801970	*	×
652/NC/2012	Camden	North Carolina	2012	Diagnostic case	KC801971	☑	☑
654/MS/2012	Copiah	Mississippi	2012	Diagnostic case	KC801972	☑	×
655/MS/2012	Perry	Mississippi	2012	Diagnostic case	KC801973	×	×
660/SC/2012	Williamsburg	South Carolina	2012	Diagnostic case	KC801980	☑	☑
667/MS/2012	Stone	Mississippi	2012	Diagnostic case	KC801974	☑	☑

FWPV=*Fowlpox virus*; REV=*Reticuloendotheliosis virus*; *=not tested; ×=negative; ☑=positive.

[a] Virus identification: case number/state of collection/year of collection.
[b] Collection method: Diagnostic clinical case (entire bird) or seasonally harvested sample (liver only).
[c] Other than the index case 12/AR/2009, GenBank accession numbers refer to p31/capsid sequences.

1983), suggesting that the natural host range of the virus may be restricted to birds of the order Galliformes, which also includes other game birds such as pheasants, quail, and grouse; however, reports of natural LPDV infections have been limited to domestic turkeys. Under experimental conditions, viremia occurs approximately two weeks after infection and may last for up to 10 months (Zimber et al., 1983) and horizontal transmission can occur among birds in close contact (McDougall et al., 1978). How the virus is transmitted in nature (e.g., vector-borne, horizontal/vertical transmission) is uncertain.

Diagnostically, the identification of LPDV has been hampered by the inability to isolate and propagate the virus in an appropriate culture system, including embryonating eggs, primary cell cultures, and established cell lines (Gazit and Yaniv, 1999). However, inoculation of naive turkeys with lymphocytes transfected with an infectious clone resulted in the reproduction of disease