BK and Other Polyomaviruses in Kidney Transplantation

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Summary: For more than 40 years, polyomaviruses (BK virus and JC virus) have been known to cause disease in human beings. Recently, 11 new polyomaviruses were discovered. However, the majority of these viruses are rare in renal transplant recipients and BK and JC viruses remain the most important polyomaviruses to impact this population. BK virus presents as BK virus nephropathy and has, in rare instances, been associated with hemorrhagic cystitis or ureteral strictures. JC virus can cause progressive multifocal leukoencephalopathy or nephropathy in this population as well, but is uncommon. Antiviral prophylactic and therapeutic interventions for these diseases are lacking to date, although reduction of immunosuppression has been associated with success in treating both BK virus nephropathy and JC virus–induced disease. Risk factors are not well defined and vary across studies. However, the cumulative degree of immunosuppression is regarded universally as an important contributor to BK virus replication. For these reasons, it is recommended to screen all renal transplant recipients prospectively for BK virus infection. Multicenter trials using standardized BK and JC virus screening methods are necessary to define risk factors better, and to determine the effect of prophylaxis and treatments for these polyomaviruses affecting renal transplant recipients.

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The human polyomaviruses are ubiquitous, small (40-45 nm), circular, nonenveloped icosahedral capsids containing double-stranded DNA genomes of approximately 5,000 base pairs.[1] Polyomaviruses used to be classified with the papillomaviruses in the family Papovaviridae, however, they more recently have undergone re-reclassification under a new designation of *Polyomaviridae family*, which includes polyomavirus as the only genus.[2]

The genomes of polyomaviruses can be divided functionally into three regions: the early, the late, and the transcriptional control regions.[1,3] The early region codes for two main nonstructural proteins, large T-antigen and small t-antigen, which regulate viral DNA replication and control the viral lytic cycle; these have many effects on host cellular pathways, including DNA repair and cell-cycle progression. The late region codes for the three structural proteins, known as viral capsid proteins (VP)-1, VP-2, and VP-3. BK and JC polyomaviruses also contain agnoprotein in the late gene region, which is responsible for viral capsid assembly and virion release from infected cells.[4] The noncoding control region contains the origin of replication and regulatory regions that direct viral transcription.[1,3] This becomes clinically relevant when laboratories used to monitor BK virus loads use different primers such as BK virus large T antigen or VP-1, which can result in variability in BK virus assay results.[5,6]

TYPES OF POLYOMAVIRUSES

For more than 4 decades, two polyomaviruses, BK and JC, were thought to cause all disease in human beings. A third polyomavirus, Simian virus-40 (SV-40), a monkey polyomavirus, was thought to be introduced into the human population through unrecognized contamination in polio vaccines, and was discovered in 1960.[7] However, its classification as a human polyomavirus still is widely debated.[8] BK virus (named after the initials of the first patient in whom it was discovered), first was reported in 1971 in a renal transplant recipient with a ureteric stricture.[9] That same year, JC virus (also named after the initials of the patient in whom it was discovered), was reported in a patient with Hodgkin's lymphoma and progressive multifocal leukoencephalopathy (PML).[10]

More recently, as a result of advances in genomic sequencing technologies, at least 11 additional polyomaviruses have been identified as affecting human beings, bringing the total to 14 viruses if SV−40 is included as affecting human beings.[11] A descriptive summary of the viruses can be found in Table 1.[9,10,12–22] These include human polyomavirus 3 (KI virus), named after the institution of discovery, the Karolinska Institute in

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Table 1. Known Human Polyomaviruses[9,10,12–22]

Genus	Species	Abbreviation	Human Polyomavirus Numeric Assignment	Disease Associated With Virus	Year Description of Virus First Published	Reported to Have Been Detected in Renal Transplant Recipients
Orthopolyomavirus	BK polyomavirus	BKPyV	Human polyomavirus 1	Nephropathy Hemorrhagic cystitis Ureteric strictures	1971[9]	X
	JC polyomavirus	JCPyV	Human polyomavirus 2	PML Nephropathy	1971[10]	X
	Merkel cell polyomavirus	MCPyV	Human polyomavirus 5	Merkel cell carcinoma	2008[14]	X
	Trichodysplasia spinulosa–associated polyomavirus	TSPyV	Human polyomavirus 8	Trichodysplasia spinulosa	2010[16]	X
	Malawi polyomavirus and Mexico polyomavirus	MWPyV and MXPyV	Human polyomavirus 10 (HPyV10)	None known Possibly associated with diarrhea	2012[18,19]	
	Saint Louis polyomavirus	STLPyV	Human polyomavirus 11 (HPyV11)	None known	2013[20]	
	Human polyomavirus 9	HPyV9	Human polyomavirus 9 (HPyV9)	None known	2011[17]	X
	New Jersey polyomavirus	NJPyV	Human polyomavirus 13 (HPyV13)	Vasculitis, myositis, and retinal blindness in a pancreas transplant recipient	2014[22]	
Wukipolyomavirus	Human polyomavirus 6	HPyV6	Human polyomavirus 6 (HPyV6)	None known	2010[15]	
	Human polyomavirus 7	HPyV7	Human polyomavirus 7 (HPyV7)	Rash and viremia in lung transplant recipient	2010[15]	
	Washington University polyomavirus	WUPyV	Human polyomavirus 4	None known	2007[13]	
	Karolinska Institute polyomavirus	KIPyV	Human polyomavirus 3	None known	2007[12]	
Not yet determined	Human polyomavirus 12	HPyV12	Human polyomavirus 12	None known	2013[21]	X

Because its presence in the human population still is debated, SV-40 is not included in this table. Viruses that have been reported to have been detected in renal transplant recipients are marked with an X.

Stockholm Sweden,[12] and human polyomavirus 4 (WU virus),[13] named after Washington University in Saint Louis, Missouri, where it was discovered. Both viruses were found in respiratory secretions and reported in the literature in 2007. Human polyomavirus 5 (Merkel cell polyomavirus) was reported in 2008 after it was detected in a patient with Merkel cell carcinoma.[14] Of note, there also have been reports of this rare virus occurring in renal transplant recipients.[23] Discovery of human polyomavirus 6 and 7 also were reported in 2010, but were not associated with any disease to date at that time.[15] However, human polyomavirus 7 has since been reported to be