



## JC Polyoma virus (JCV)

JC Polyoma virus (JCV) is a small double-stranded DNA virus originally isolated from brain lesions of a patient with progressive multifocal leukoencephalopathy (PML). It was subsequently named from the initials of this patient, John Cunningham<sup>1,2</sup>. JCV has a prevalence of over 80% in the general population<sup>3</sup> and primary infection usually occurs early in life<sup>4</sup>. JCV is the causative agent for PML, and has been linked some haematological diseases as well as in some autoimmune diseases treated with certain lymphocyte-specific antibodies.

### **Structure and genome**

JCV belongs to the family of Polyomaviridae (formerly known as Papoviridae) which comprises at least 16 members. The name polyoma reflects the ability of some polyomaviruses to produce multiple (poly-) tumours (-oma). Polyomaviruses are further subdivided into 3 genera<sup>5</sup>: Orthopolyomavirus (JCV, BKPyV, SV40, MCPyV...), Wukipolyomavirus (KIPyV, WUPyV, HPyV6, HPyV7), and Avipolyomavirus (avian polyomaviruses).

Polyomaviruses are small (40-50nm), non-enveloped, icosahedral viruses containing a small circular double-stranded DNA genome of around 5,000bp. The genome encodes 6 genes: large T, small t, viral protein 1 (VP1), viral protein 2 (VP2), viral protein 3 (VP3) and agnoprotein, where VP1-3 form the capsid.

### **Molecular and cellular pathophysiology**

Cell entry is mediated via interaction of JCV's VP1 protein with sialic acid residues of gangliosides (GT1b) on the cell surface. The virus is then endocytosed and exported to the nucleus where it replicates. Viral replication occurs through the transcription of the non-structural proteins (early phase) followed by transcription of the capsid proteins (late phase) using the cellular machinery. VP1 also interacts with the serotonin receptor 5HT2AR<sup>6</sup>, expressed on glial cells (oligodendrocytes and astrocytes) and kidney cells, consistent with the main sites of JCV infection.

Since primary infection is usually asymptomatic, the exact mode of transmission still remains controversial, although JC virions have been detected in tonsillar stromal cells and in B cells from tonsil tissue, it is believed that JCV is spread via respiratory inhalation or oral contact, with the initial site of infection likely to be the tonsils<sup>7</sup>. Following an asymptomatic primary infection usually occurring in early childhood, a life-long latent JCV infection will persist at subclinical levels, resulting in occasional shedding of virus particles in the urine even in healthy individuals. The main cell

types which will remain persistently infected by JCV are kidney epithelial cells, oligodendrocytes and to a lesser extent, B-lymphocytes.

## **Epidemiology**

JCV is very common in the general population, infecting 70 to 90 percent of humans, and primary infection usually occurs in childhood or adolescence<sup>3</sup>. Since minor sequence differences have been found in various geographic areas, JCV has been classified in 8 different subtypes, although no link between genotype and virulence has been established to date:

- Types 1 and 4 are found in Europe and are closely related.
- Type 2 has several variants: subtype 2A is found mainly in the Japanese population; 2B in Eurasians; 2D in Indians and 2E is found in Australians.
- Types 3 and 6 are found in Africa.
- Subtypes 7A, B and C are found in China, Mongolia and South-East Asia.
- Subtype 8 is found in Papua New Guinea and the Pacific Islands.
- Subtype 5 is a recombinant between 2B and 6.

## **JCV in disease**

JCV is the etiologic agent of progressive multifocal leukoencephalopathy (PML) which is an often fatal demyelinating disease of the CNS. It is characterised by widespread brain lesions due to the infection and destruction of oligodendrocytes and subsequent loss of the myelin sheath. Symptoms include weakness or paralysis, loss of vision, impaired speech and cognitive deterioration. PML occurs almost exclusively in immunodeficient individuals, such as patients with AIDS, haematological and lymphoreticular malignancies, autoimmune rheumatological diseases or those undergoing organ transplantation. Some patients receiving monoclonal antibodies-based immune therapy have also been reported to develop PML. These include natalizumab for multiple sclerosis and Crohn's disease, rituximab for B cell lymphomas, efalizumab for psoriasis, or brentuximab for Hodgkin's lymphoma.

JCV has also been linked to nephropathy in the context of renal transplantation, although much less frequently than BKV<sup>8,9,10</sup>. Similarly, BKV has also been reported to be able to cause a PML-like disease<sup>11</sup>.

Both JCV and BKV have also been detected in some breast carcinomas but the relevance of these findings on a direct role of these polyomaviruses in breast cancer remains to be elucidated<sup>12</sup>. Other studies have suggested that JCV may be linked to colorectal cancer, as JCV has been detected in malignant colon tumours, but these findings are still controversial<sup>13</sup>.

## **Treatment**

Although there is no treatment currently available for PML<sup>14</sup>, the advent of highly active anti retroviral therapy (HAART) in the treatment of HIV infection has greatly reduced the impact of PML in AIDS patients. Since immunodeficiency causes this virus to progress to PML, immunosuppressants are contraindicative to those infected, and disease progression may slow or even stop if the patient's immune system improves.

Despite the lack of treatment for PML, the antimalarial drug Mefloquine, which targets the 5-HT<sub>2A</sub> serotonin receptor, was reported to have successfully eliminated JCV from a PML patient thereby preventing further neuronal deterioration<sup>15</sup>. Although preventing virus entry through the serotonin receptor sounded promising, these results were disappointed by a subsequent studies<sup>17</sup>.

More recently, recombinant IL-7 has also provided very promising results in a patient with PML and idiopathic CD4+ T-cell lymphocytopenia<sup>17</sup>. A further study showed similar results in two patients treated with rIL-7, and JCV VP-1 protein<sup>18</sup>. Further clinical studies are currently ongoing to confirm these results and better understand the mechanism of IL-7 in removing JCV infection from the brain.

### **Clinical diagnostics**

The diagnosis of JCV infection almost always occurs after the primary infection as it is either asymptomatic or sub-clinical. Detecting JCV infection is particularly relevant in assessing the potential risk of PML development in AIDS patients as well as in patients with Crohn or multiple sclerosis (MS) receiving Natalizumab.

Traditionally, PML diagnosis relied on histopathology and electron microscopy of brain biopsies. As mentioned earlier, PML is characterised by oligodendrocytes with enlarged nuclei containing filamentous arrays of polyomavirus particles. During active JCV infection, these oligodendrocytes are lysed, leading to the loss of the myelin sheath. Foci of demyelination occur randomly in the white matter and can usually be seen on MRI images. However, since brain lesions might not be visible during the early stages of infection, detection of JCV in CSF or on brain biopsies provides a more specific, more sensitive and non-invasive means of establishing an early PML diagnosis.

At Micropathology Ltd, we use a TaqMan hydrolysis probe assay targeting the small T antigen of human JCV. The primers and probes used are specific for all published JCV strains and do not cross react with any virus potentially present in relevant clinical specimens (Adenovirus, HSV1-2, VZV, EBV, CMV, HHV6-8, enteroviruses and parechovirus) or with other polyomaviruses (BKV, KIPV, WUPV, MCPV). Using a logistic regression model, the analytical sensitivity (95%) was determined to be 104 JCV DNA copies/mL, with a 95% confidence interval ranging from 46-260 JCV DNA copies/mL. we perform a routine surveillance of public databases to ensure optimal assay performance against newly published and relevant variants.

For additional information regarding the JCV assay, please contact Dr Ronan Calvez, [R.Calvez@Micropathology.com](mailto:R.Calvez@Micropathology.com).

### **Sample material**

- CSF
- Whole Blood
- Urine
- Biopsies

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