

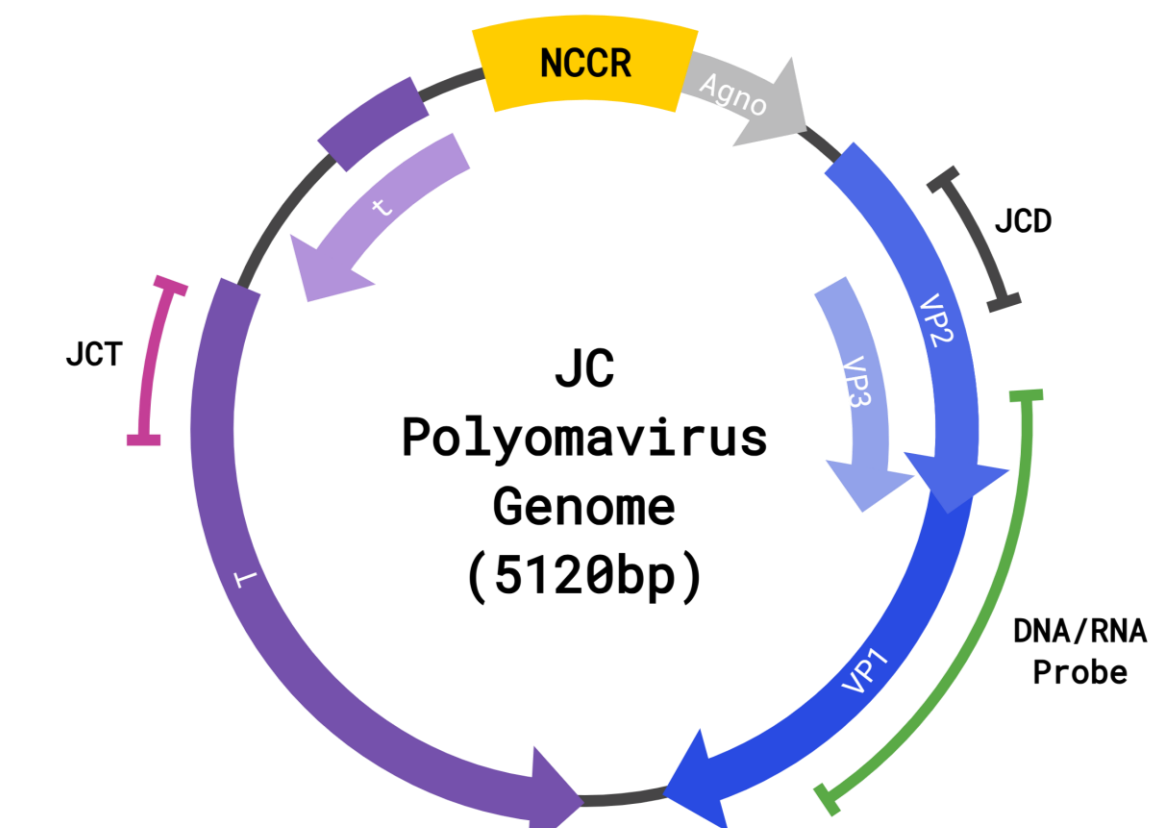
# JC Polyomavirus Noncoding Control Region Affects Cell Tropism in Central Nervous System and Kidney

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## Introduction

JC Polyomavirus (JCPyV) infects 40-60% of the population worldwide. In healthy individuals, it is asymptomatic and takes residence in the kidney with occasional shedding in the urine. In immunocompromised patients it can travel to the central nervous system (CNS) causing a debilitating and often lethal infection known as Progressive Multifocal Leukoencephalopathy (PML). There is no available treatment for JCPyV and patients who survive the infection are left with severe neurological deficits<sup>1</sup>.

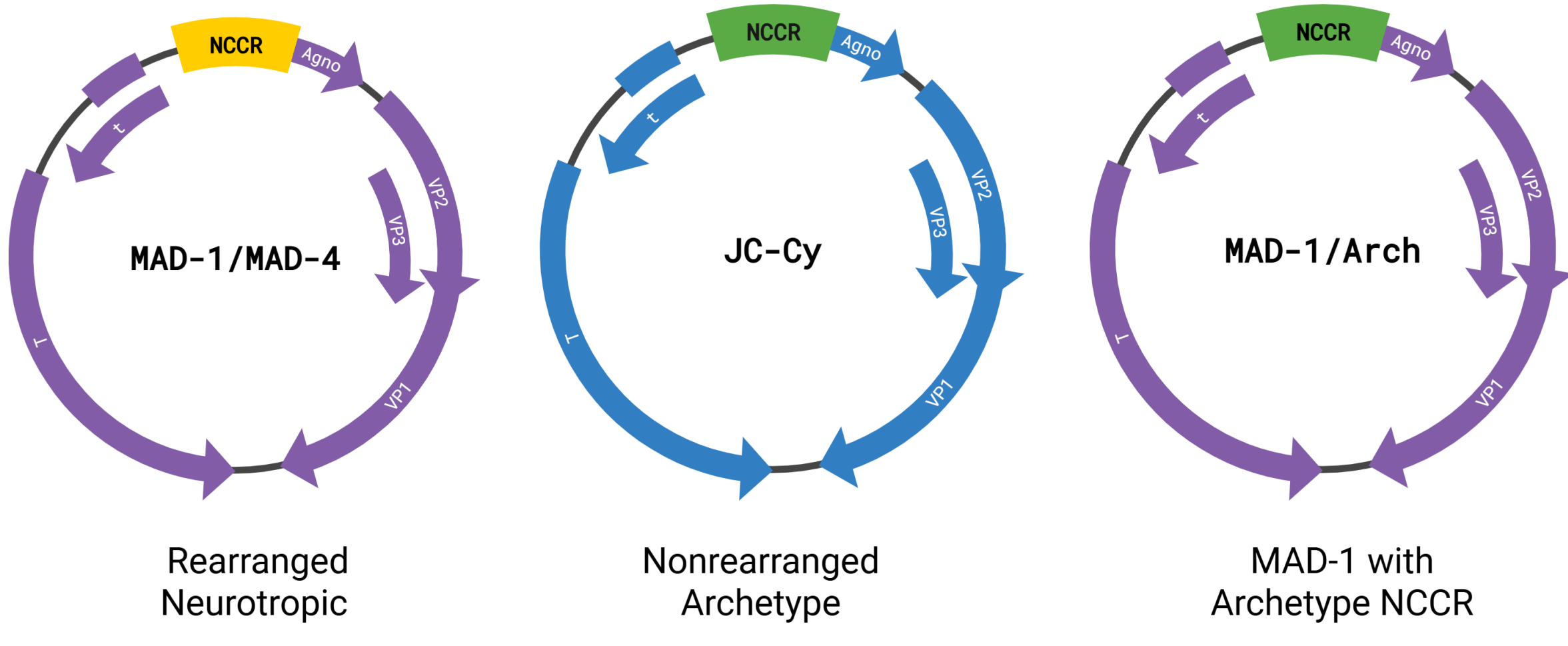


**Figure 1. Simplified diagram of JCPyV genome** Early genes are given in purple and late genes in blue. Regions of PCR amplification (JCD and JCT) and probe detection are given.

Progression to neurologic disease is thought to be associated with rearrangement of the noncoding control region (NCCR). Cases of PML and Granule Cell Neuronopathy (GCN) generally contain several insertions and deletions in this region while virus in the kidney known as archetype does not contain these changes<sup>2,3</sup>. Our lab recently reported a case of JCPyV associated meningoencephalopathy caused by a strain of JCPyV containing an archetype NCCR<sup>4</sup>. Here we present follow up studies that explore the role of NCCR rearrangement on cell infection and viral protein expression in the kidney and CNS.



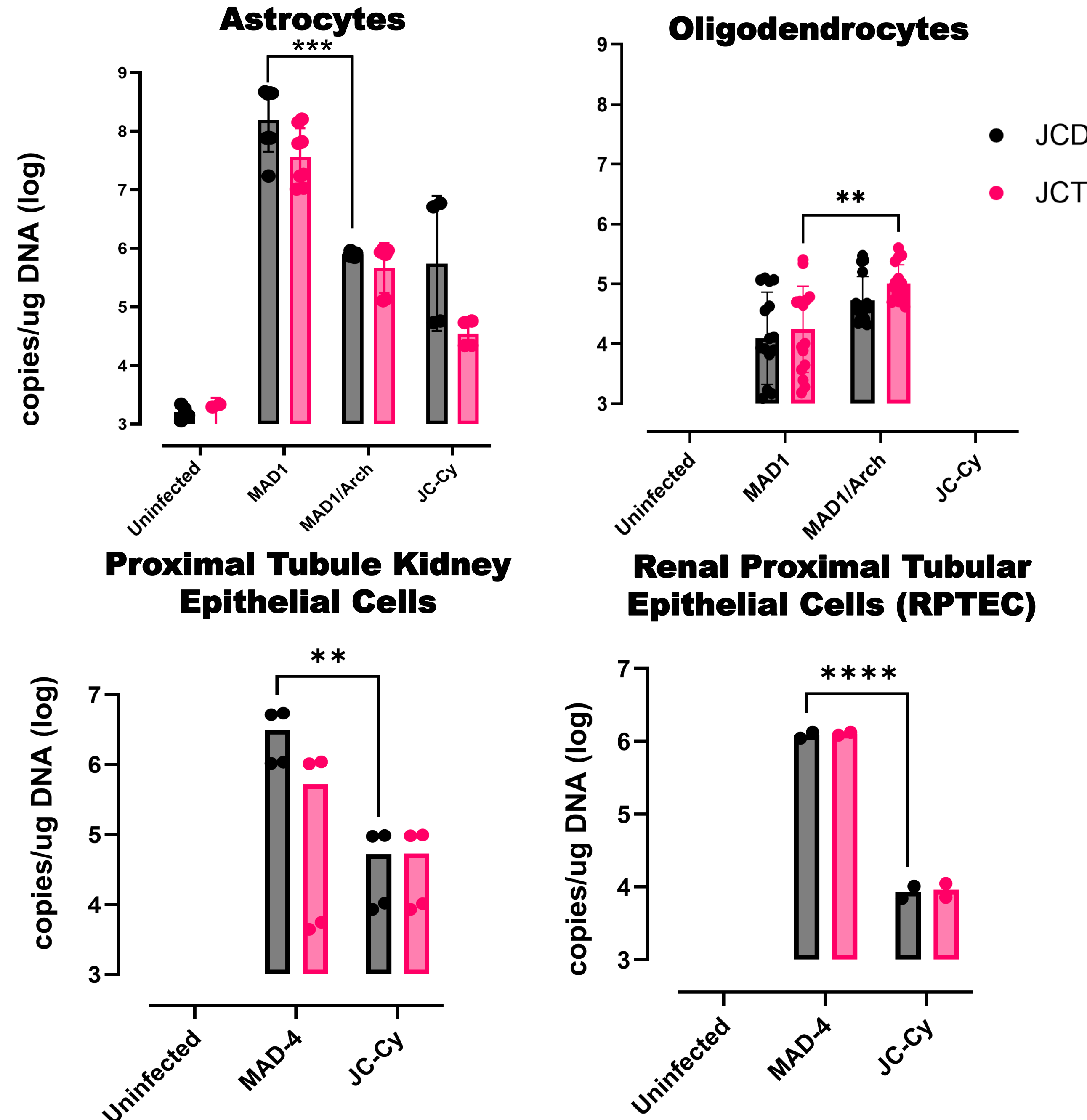
**Figure 2. NCCR rearrangement is associated with diseases.** The NCCR is divided into six segments according to previous classifications<sup>5</sup>. Variations in the rearranged NCCRs is detected in clinical isolates from PML, GCN, Hemorrhagic White Matter (HWM) and our case study<sup>3,6-9</sup>.



**Figure 3. JCPyV variants.** We used wildtype strains of archetype (JC-Cy) and neurotropic JCPyV (MAD-1, MAD-4) with nonrearranged and rearranged NCCR, respectively, as well as a hybrid neurotropic virus with a nonrearranged NCCR (MAD-1/Arch).

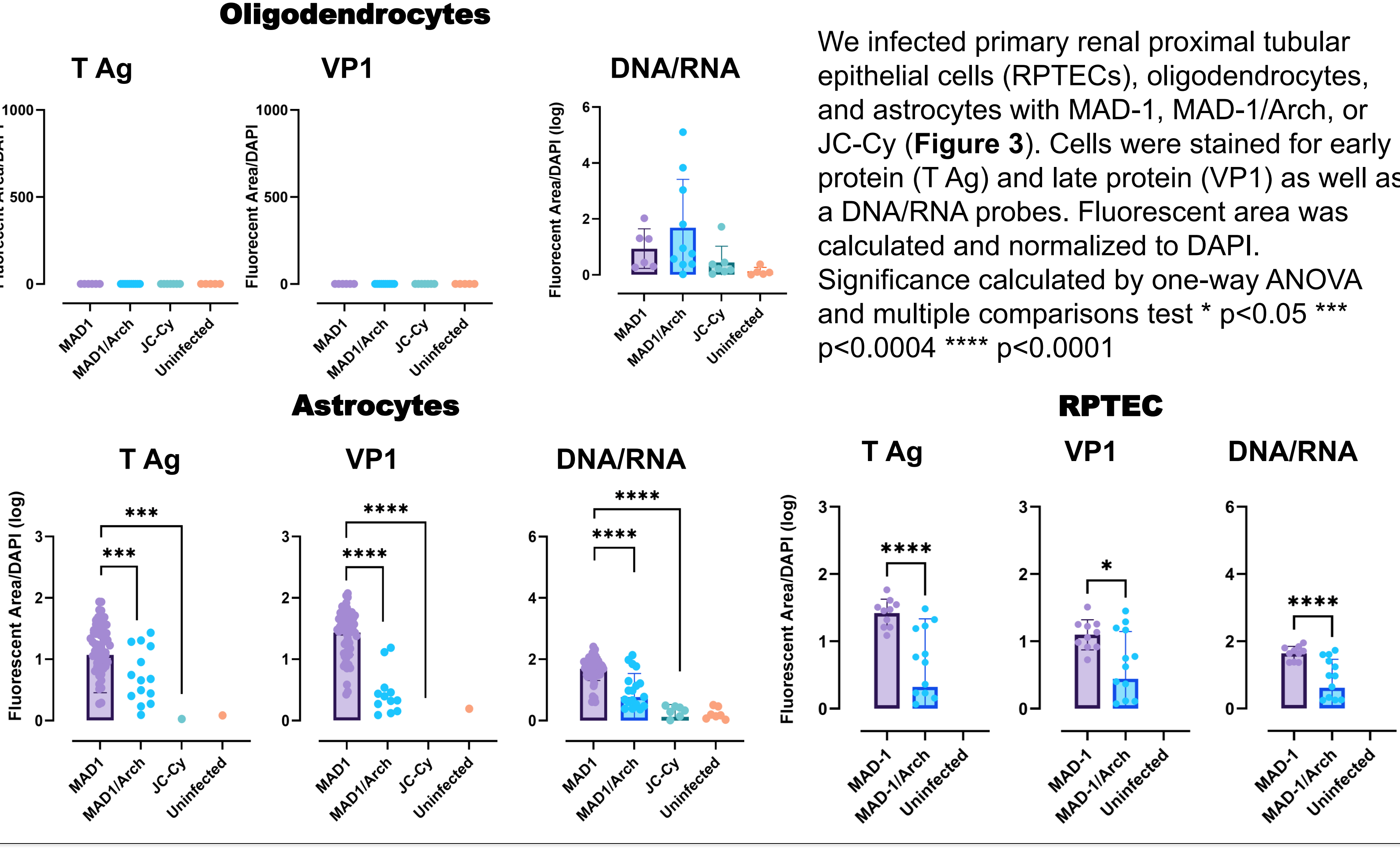
## Results

### Digital Nanodrop PCR

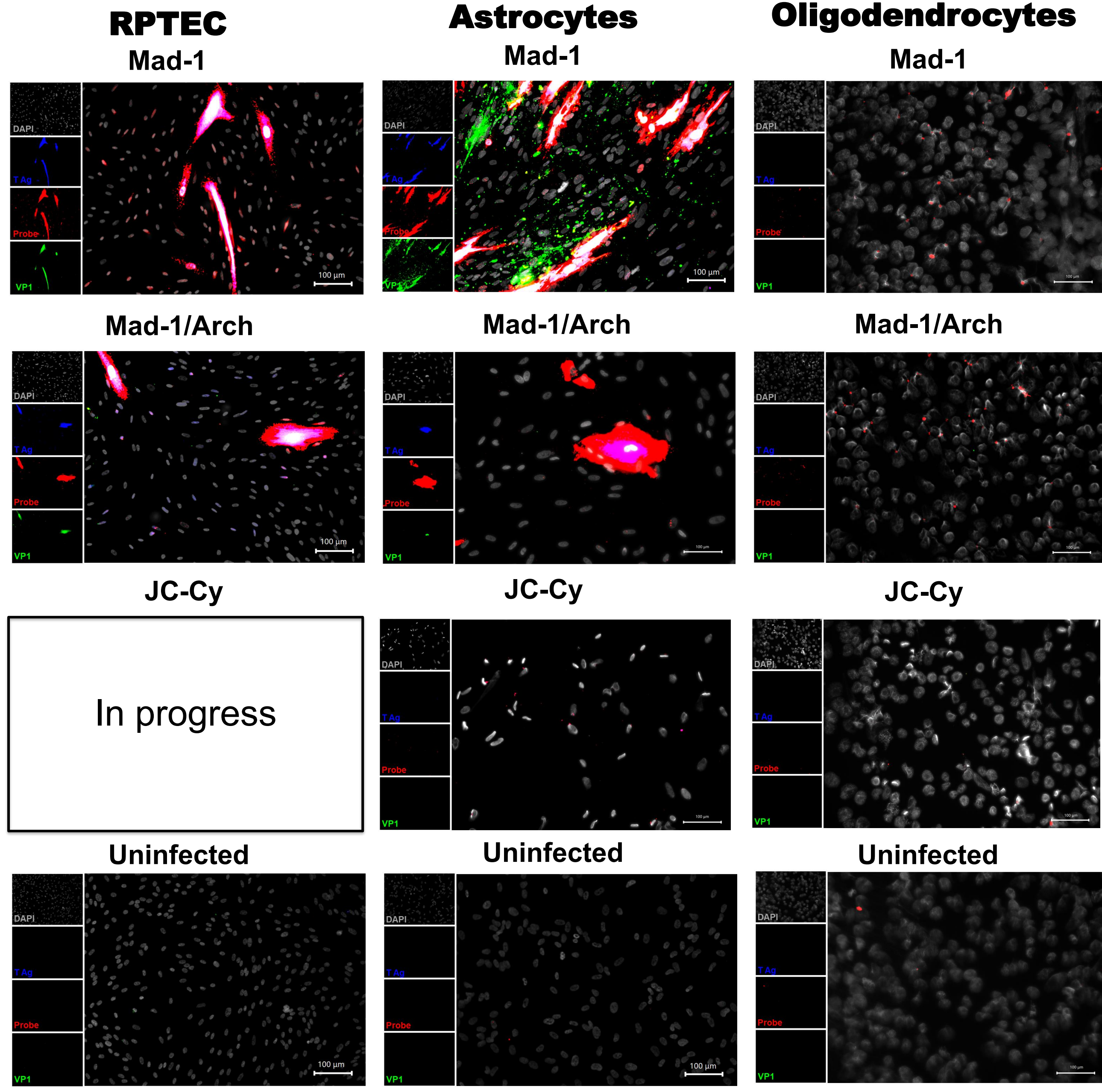


We infected primary kidney cells, astrocytes and oligodendrocytes with MAD1 (or MAD4), MAD1/Arch hybrid, or JC-Cy (**Figure 3**). Infection was detected by amplifying two regions of the genome named JCD and JCT (**Figure 1**) using digital nanoplate PCR. Kidney cells had increased infection with MAD-4 and detectable infection with JC-Cy. Astrocytes had increased infection with MAD1 compared to JC-Cy and MAD1/Arch while Oligodendrocytes had increased infection with MAD1/Arch and low to undetectable levels of JC-Cy.

### Immunofluorescence and RNAscope



## Results Continued



**Immunofluorescence** Images were taken at 20x on a Keyence BZ-X800 microscope and imaging setting were kept consistent across specimens.

## Conclusions

- Rearrangements in the NCCR allow JCPyV to replicate more effectively in kidney cells and astrocytes.
- Virus can enter oligodendrocytes but does not appear to replicate. Entry is enhanced in neurotropic strains of virus but does not appear to be influenced by NCCR rearrangements.
- Rearranged NCCR appears to lead to increased release of virus outside of the cell and expression of late proteins in astrocytes.
- Astrocyte infection may be more responsible for JCPyV pathology than oligodendrocytes.

## Future Directions

- Identify changes in host cell response to NCCR rearrangements.
- Investigate whether changes in NCCR result in release of free virus or extracellular vesicle associated virus.
- Identify how cell tropism correlates to demyelination during PML
- Elucidate the life cycle of JCPyV including where NCCR rearrangement occurs and when the virus reaches the CNS.
- Identify host factors that encourage NCCR rearrangement

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