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Macaques Exhibit TDP-43 Morphology Comparable to Human Aging and Dementia

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Abstract

Transactive response DNA binding protein of 43 kDa (TDP-43) is a ubiquitously expressed nuclear protein involved in RNA metabolism and stress granule formation. Pathological inclusions and mislocalization of this protein in brain cells is pathognomonic or concurrent across a wide range of neurodegenerative diseases, and has been implicated in age-associated cognitive decline. In these pathologies, TDP-43 becomes mislocalized, forming inclusions in the cytoplasm, nucleus, and cell processes. In these inclusions, TDP-43 undergoes aberrant post-translational modifications, often phosphorylation. This investigation assessed the presence of TDP-43 pathology and mislocalization in the amygdala, entorhinal cortex, and prefrontal cortex of aged rhesus macaques. Endogenous TDP-43 pathology in the macaque brain has not been well described. We hypothesized that the macaque exhibits histological TDP-43 phenotypes resembling those found in human neurodegeneration and cognitive decline. To test our hypothesis, we used immunohistochemistry to examine the presence, location, and morphology of native TDP-43 and phosphorylated-TDP-43 (ser409/410) in rhesus macaques aged 6 to 30 years. We describe a variety of distinct inclusion morphologies, most notably in the amygdala and entorhinal cortex. Whether the TDP-43 morphologies we observed in the macaque are abnormal, indicative of cognitive decline, or neurodegeneration has not been fully elucidated. However, many of these morphologies resembled those observed in human neurodegeneration and aging. These observations lay the ground work for the rhesus macaque as a highly translational animal model of human aging with respect to TDP-43.