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Research Report

Expression of PINK1 mRNA in human and rodent brain and in Parkinson's disease

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ABSTRACT

Mutations in *PINK1* (PTEN-induced putative kinase 1) are causal for early onset recessive parkinsonism in humans, characterized by damage to the nigrostriatal system. *In situ* hybridization studies in rodent brains have suggested a predominantly neuronal expression of PINK1 mRNA but immunocytochemistry of human brain tissue has shown PINK1-like immunoreactivity in both neurons and glia. In this study, we assessed the comparative distribution of PINK1 mRNA in human, rat and mouse brain. We observe that in humans PINK1 message is expressed in neurons with very little to no signal in glia and confirms similar findings in rodent tissue. Highest levels of expression were observed in hippocampus, substantia nigra and cerebellar Purkinje cells. We also show that PINK1 mRNA expression is similar in nigral neurons from neurologically normal controls and sporadic Parkinson's disease cases.

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1. Introduction

PTEN-induced putative kinase (*PINK1*) mutations are a rare cause of recessive parkinsonism (Valente et al., 2004). Although the detailed neuropathology of *PINK1* mutation carriers is not known, patients show decreased DAT ligand binding in striatum, assessed by PET and SPECT (Albanese et al., 2005; Khan et al., 2002). This suggests a loss of the dopamine projection neurons from substantia nigra (SN) to putamen, in common with findings in other familial parkinsonism genes (reviewed by Cookson, 2005).

The *PINK1* gene encodes a 581-amino-acid protein with a serine/threonine kinase domain preceded by an N-terminal mitochondrial targeting peptide (Valente et al., 2004). The kinase activity (Beilina et al., 2005; Unoki and Nakamura, 2001) and mitochondrial localization (Beilina et al., 2005; Silvestri et al., 2005) of the PINK1 protein have been confirmed in transfected cells. PINK1 kinase protects cells from caspase-induced toxicity by decreasing cytochrome *c* release (Petit et al., 2005), while loss of PINK1 activity leads to increased levels of lipid peroxidation and decreased complex I function (Hoepken et al., 2007). The mechanism(s) by which PINK1 exerts these beneficial effects and, in particular, what the substrates are for the kinase, are not known.

All genes linked to inherited parkinsonism identified to date are expressed in the brain and in other tissues (Bader et al., 2005; D'Agata et al., 2000; Galter et al., 2006; Horowitz et al., 1999; Shang et al., 2004; Shimura et al., 1999; Solano et al., 2000; Stichel et al., 2000). Northern blot analyses have suggested that the same is true for PINK1, as expression is

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seen in most tissues and brain regions (Nakajima et al., 2003; Unoki and Nakamura, 2001). *In situ* hybridization of PINK1 in mouse and rat tissue revealed hybridization consistent with a roughly even neuronal expression of PINK1 throughout the brain (Taymans et al., 2006). Immunolabeling of human PD and control brain, however, suggests that PINK1 is expressed in both neurons and glia (Gandhi et al., 2006). Although the pattern of immunolabeling in human brains is consistent with mitochondrial localization, PINK1 immunoreactivity is also reported in 5–10% of Lewy Bodies in the brain stem (Gandhi et al., 2006) and cortex (Murakami et al., 2007) and in glial cytoplasmic inclusions (GCIs, Murakami et al., 2007). As Lewy bodies and GCIs are cytoplasmic inclusion bodies characteristic of Parkinson's disease and multiple system atrophy respectively, these studies imply that PINK1 may have extra-mitochondrial localization, which has also been seen at very high expression levels *in vitro* (Beilina et al., 2005), or that mitochondria are components of intracellular inclusion bodies, as has been suggested before (Zhu et al., 2003). There is also some evidence that PINK1 protein levels may be higher in cases with sporadic Parkinson's disease compared to neurologically normal controls (Gandhi et al., 2006).

The question of which cells express PINK1 in humans remains unresolved. PINK1 mRNA distribution was analyzed in rodents while PINK1 protein was analyzed in human tissue. It is thus unclear whether the apparent discrepancies between protein and mRNA expression are due to differences between species, the techniques used, or whether PINK1 protein can relocalize post-translationally from neurons to glia. Here, we confirm the reported mRNA expression in rat and mouse brain and provide novel *in situ* hybridization evidence demonstrating mRNA expression of PINK1 in human brain. We also compare expression in sporadic Parkinson's disease compared to neurologically normal controls.

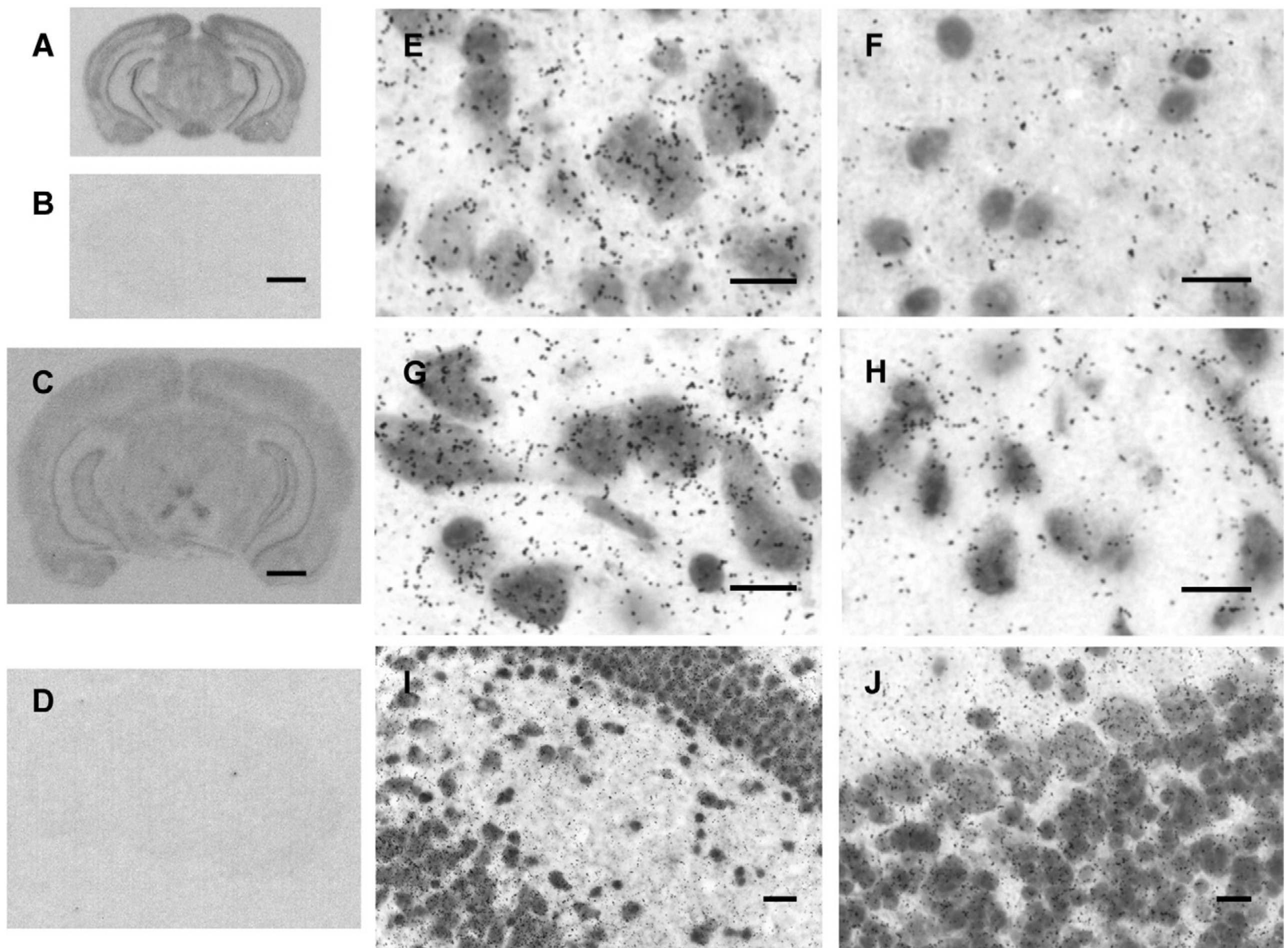

Fig. 1 – Expression of PINK1 mRNA in mouse and rat brain. Phosphoimages of coronal sections of (A) mouse and (C) rat brain hybridized with PINK1-specific radioactively labeled oligonucleotides, showing low power views of PINK1 mRNA hybridization patterns. Random oligonucleotide controls for (B) mouse and (D) rat, suggest specificity of the PINK1 signal. (E–J) Emulsion dipped slides were used to evaluate cellular expression in mouse brain (rat data were similar; not shown). (E) Cortical neurons showed moderate PINK1 expression, while (F) subcortical glia show staining similar to background. (G) Substantia nigra and (H) VTA neurons show strong hybridization signals. (I) Both the hilus region of hippocampus and the dentate gyrus show substantial PINK1 mRNA expression. (J) Purkinje cells of the cerebellum show strong PINK1 hybridization. Scale bars: A–D, 2 mm; E–J, 20 μm.

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