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Polynucleotide kinase phosphatase (PNKP) in neuropathological diseases

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DNA is a target of various damaging agents such as reactive oxygen species, ionizing radiation, or abortive topoisomerase activity. These events often result in non-conventional DNA termini, which must be processed before repair of the lesion can be completed. Interestingly, hereditary defects in DNA end processing often result in neuropathological disorders. Polynucleotide kinase phosphatase (PNKP), one of the DNA end processing factors, employs DNA 3'-phosphatase and DNA 5'-kinase activities to form ligatable DNA ends, and is recruited to DNA breaks via protein-protein interactions mediated by an amino-terminal fork-head associated (FHA) domain. Mutations in PNKP are associated with both *microcephaly with early onset seizures* (MCSZ) and *ataxia with oculomotor apraxia 4* (AOA4). However, how mutations in the same gene can result in two different diseases is unknown. Here, to address this question, we have begun to examine the importance of the different protein domains/activities in PNKP in human cells for DNA strand break repair, and to measure these activities in fibroblasts from patients harbouring PNKP mutations. Our current data addressing this question will be described.

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