LETTER TO THE EDITOR

A single strand that links multiple neuropathologies in human disease

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Sir, We read with great interest the review by Reynolds and Stewart (2013) in the January issue of *Brain* reviewing three neurological disorders associated with defective single strand break repair: ataxia oculomotor apraxia 1 (AOA1), spinocerebellar ataxia with axonal neuropathy 1 (SCAN1) and microcephaly, early-onset, intractable seizures and developmental delay (MCSZ) syndrome. The authors discuss in detail the clinical features and underlying pathological mechanisms. We noted that they focus on the differences in clinical presentation between AOA1, SCAN1 and MCSZ syndrome; the first two having progressive cerebellar ataxia as a major symptom, and the latter retaining normal brain structures and lacking signs of neurodegeneration or ataxia. They hypothesize that the hypomorphic nature of the mutation with preservation of DNA 3’ phosphatase activity of PNKP leads to this attenuated phenotype.

Indeed, the individuals described in the first report of MCSZ syndrome lack cerebellar symptoms (Shen et al., 2010). However our group recently published clinical details of two brothers with PNKP mutation who, besides the congenital microcephaly, presented in early childhood with a neurodegenerative disorder consisting of progressive cerebellar ataxia and severe polyneuropathy leading to loss of motor milestones, wheelchair dependence, and in one, premature death at the age of 25 years (Poulton et al., 2013). Intensive investigations including repeated brain imaging and EMGs showed progressive cerebellar atrophy and severe mixed demyelinating/axonal sensorimotor polyneuropathy (Fig. 1). In addition they had mild epilepsy, not meeting criteria for early infantile epileptic encephalopathy, and moderate/severe intellectual disability. Through homozygosity mapping and whole genome sequencing, a homozygous mutation (c.1250_1266dup resulting in a frameshift p.Thr424GlyfsX48) in PNKP was identified. This is exactly the same homozygous duplication already described in the three patients with MCSZ syndrome who did not show any evidence of neurodegeneration (Shen et al., 2010). In light of the knowledge of the PNKP function we can fully explain the phenotype of our patients and agree with the prediction that this protein plays a major role in development of the CNS and in maintenance of normal functions of both CNS and PNS throughout life.

PNKP is a dual function enzyme that functions in both single strand and double strand break repair. PNKP directly interacts with TDP1, associated with SCAN1, and this has led to the previous suggestion that PNKP could be a candidate gene for spinocerebellar ataxia with neuropathy (Plo et al., 2003). PNKP is involved in single strand break DNA repair by binding to a scaffold provided by XRCC1 and processing the repaired strands for the DNA ligase LIG3 (Caldecott, 2008). Interestingly, XRCC1 knock-out mice show loss of cerebellar purkinje cells, ataxia and seizures (Lee et al., 2009).

PNKP is also involved in double strand base repair and directly interacts with XRCC4 to activate LIG4. Conditional knock-out mice (*Lig4 Nes-Cres*) show microcephaly and have increased apoptosis in the brain at E23.5-E15 (Gatz et al., 2011).

There is therefore sufficient knowledge to support and to expect the presentation of microcephaly, cerebellar ataxia and polyneuropathy, which we observed in case of PNKP mutation. We showed in patient-derived fibroblasts harbouring the PNKP duplication an increased tendency to undergo apoptosis, thus supporting the theory that their microcephaly is caused by an increased apoptosis in neuronal precursors with unrepaired DNA...
breaks. We hypothesize that PNKP’s dual function in single and double strand breaks explains the combination of cerebellar atrophy and microcephaly.

It is not clear at the moment why the neurodegenerative symptoms were not present in the early description of the same PNKP mutation, but this is interesting to address in future studies, particularly whether additional genetic, epigenetic or environmental factors contribute to this variability, as some of these could be modifiable and amenable to intervention.

References


Figure 1 Brain sagittal T1 MRI of one of the brothers (A), aged 16, showing microcephaly and profound cerebellar atrophy compared with an age-matched control (B).