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Zfp423/ZNF423 regulates Purkinje cell and cerebellar nuclei development

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The Zfp423/ZNF423 gene encodes a 30-zinc-finger transcription factor involved in key developmental pathways. Although null Zfp423 mutants develop cerebellar malformations, the underlying mechanism is only partially characterized. In humans, ZNF423 mutations are associated with cerebellar vermis hypoplasia and Joubert Syndrome (JS), a ciliopathy causing congenital ataxia. ZNF423 participates in the DNA-damage response (DDR), suggesting that its mutation may slow down neural progenitor cell cycle progression in cerebellar development. To characterize in vivo the function of ZFP423 in neurogenesis, we analysed allelic murine mutants in which distinct functional domains are deleted. In Purkinje cell (PC) progenitors, located in the cerebellar ventricular zone (VZ), the two mutations produce different alterations in mitotic spindle orientation, maintenance of the progenitor pool and neuronal differentiation. In both mutants, cell cycle progression is remarkably delayed and DDR markers are upregulated in VZ and rhombic lip (RL) progenitors. In the RL, Zfp423 mutants display an increase in cell death at key developmental stages, and clear alterations in cerebellar nuclei (CN) development. Our results reveal protein-domain-specific roles played by ZFP423 in different aspects of PC and CN neurogenesis, and at the same time strengthen the emerging notion that an impaired DDR may be a key factor in the pathogenesis of JS and other ciliopathies.

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