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ZFP423, a transcription factor implicated in Joubert Syndrome and Cerebellar Vermis Hypoplasia, orchestrates the pace and mode of cerebellar neurogenesis

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Neurogenesis is a tightly regulated process, both in the embryonic and in the adult brain. Its success depends on the ability of a germinative epithelium to establish the appropriate balance between maintaining an undifferentiated progenitor pool and giving birth to sequential generations of neurons and glia. The *Zfp423* gene encodes a 30 Zn-finger transcription factor (TF) which interacts with the SMAD1-SMAD4 complex (BMP signaling), Notch intracellular domain, retinoic acid receptors and Collier/Olf-1/EBF TFs. This gene has been previosly implicated in cerebellar development. Mutations in the human ortholog *ZNF423* have been identified in patients carrying cerebellar vermis hypoplasia (CVH) or Joubert Syndrome (JS), and/or exhibiting other signs of ciliopathy outside the central nervous system. We have been analyzing two mouse mutant lines carrying allelic in-frame deletions of *Zfp423*. One of them lacks Zn-finger domains 9-20 (Δ9-20), implicated in BMP and Notch signal transduction, while the other lacks a C-terminal domain (Δ28-30). Both mutants exhibit cerebellar malformations and severe ataxia. However, our results indicate that the two protein domains play sharply distinct roles in the context of cerebellar neurogenesis. In $Zfp423^{\Delta 9\text{-}20/\Delta 9\text{-}20}$ mutants, GABAergic Purkinje cell (PC) neurogenesis is impaired and the PC progenitor pool in the ventricular zone is precociously depleted. Conversely, $Zfp423^{\Delta 28\text{-}30/\Delta 28\text{-}30}$ mutants display a selective impairment in the development of glutamatergic cerebellar neurons.

References

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