

## 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 previously 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 ( $\Delta 9-20$ ), implicated in BMP and Notch signal transduction, while the other lacks a C-terminal domain ( $\Delta 28-30$ ). 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* <sup>$\Delta 9-20/\Delta 9-20$</sup>  mutants, GABAergic Purkinje cell (PC) neurogenesis is impaired and the PC progenitor pool in the ventricular zone is precociously depleted. Conversely, *Zfp423* <sup>$\Delta 28-30/\Delta 28-30$</sup>  mutants display a selective impairment in the development of glutamatergic cerebellar neurons.

### References

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### Keywords

Cerebellar organogenesis, cerebellar neurogenesis, primary cilium, ciliopathies.