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Domain-specific regulation of cerebellar morphogenesis by Zfp423 / ZNF423, a gene implicated in Joubert syndrome and cerebellar vermis hypoplasia

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The Zfp423 gene encodes a 30-Zn-finger transcription factor that acts as a scaffold for the assembly of complex transcriptional and cellular machineries regulating neural development. While null Zfp423 mutants feature a sharp decrease in the total number of cerebellar Purkinje cells (PCs), the underlying mechanisms remain unclear. Mutations of the human homolog ZNF423 have been identified in patients carrying cerebellar vermis hypoplasia (CVH) or Joubert Syndrome (JS), associated with other signs of classical ciliopathy outside the central nervous system. To further characterize the role of ZFP423 in cerebellar neurogenesis, we have performed morphological, cellular and molecular studies on two mutant mouse lines carrying allelic in-frame deletions of Zfp423. While both lines exhibit cerebellar hypoplasia, considerable differences are observed between the two mutants, with respect to neural progenitor differentiation, cell survival and morphogenesis. The results of this in vivo and in vitro structure-function analysis point to domain- and context-specific roles played by ZFP423 in different aspects of cerebellar development, and contribute to our understanding of its role as a disease / modifier gene in JS, CVH and other ciliopathies.