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Dissecting the pathogenesis of Joubert syndrome / cerebellar vermis hypoplasia in *Zfp423* mutants

The *Zfp423/ZNF423* gene encodes a 30-zinc-finger transcription factor involved in key developmental pathways. *ZNF423* mutations have been identified in individuals affected by Joubert Syndrome, a ciliopathy that causes cerebellar vermis hypoplasia and ataxia. Although *Zfp423*-null mice feature cerebellar malformations, many of the underlying developmental defects have been poorly characterized. To study *in vivo* the function of ZFP423 in central nervous system development, we analyzed allelic murine mutants in which distinct functional protein domains are deleted. Our results indicate that: 1) different ZFP423 protein domains are required for the maintenance of the Purkinje cell (PC) progenitor pool and for PC progenitor differentiation; 2) in *Zfp423* mutants, cell cycle progression is remarkably delayed and DNA damage response markers are upregulated in the cerebellar ventricular zone; 3) *Zfp423* mutants display a marked reduction of the fourth ventricle choroid plexus (ChP), revealing a near-complete lack of multiciliated ChP ependymal cells. 4) Differentiation and survival of cerebellar glutamatergic progenitors are impaired in *Zfp423* mutants, giving rise to malformed cerebellar nuclei and altered routing of their efferent tracts.