

POSTER PRESENTATION

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Coordinated epigenetic regulation of *Engrailed-1* by the chromatin remodelers *Smarca1* and *Smarca5* mediates cerebellar morphogenesis

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Background

Morphological patterning of the cerebellum requires precise changes in *Engrailed* homeotic gene expression yet the mechanisms controlling this process remain elusive. Here, we show that the *Iswi* chromatin remodeling proteins, *Smarca5* and *Smarca1*, are required for the dynamic regulation of *Engrailed-1* (*En1*). Conditional *Smarca5*-null mice display abnormal cerebellar foliation, ataxia-like symptoms and young mortality. Postnatal granule neuron progenitor expansion and Purkinje cell (PC) development are compromised and attributed to loss of *En1* expression. Mutants survive to early adulthood via upregulation of *Smarca1* and restoration of *En1* expression in PCs, while ablation of both *Iswi* genes results in lethality at birth. During late cerebellar development, we observe co-binding of the *Iswi* proteins at the *En1* locus and an altered H2AZ/H3.3 chromatin profile that accompanies changes in *En1* expression.

Materials and methods

Through mouse ES cell homologous recombination, we targeted exon 5 of the *Smarca5* gene that encodes for part of the helicase domain, thereby allowing us to conditionally ablate *Smarca5* expression in the central nervous system (CNS). We ablated *Smarca5* expression in CNS progenitors using the Nestin-Cre driver, as well as in Purkinje neurons of the cerebellum using the PCP2-Cre driver mouse line. We also ablated expression of both mammalian *Iswi* proteins by breeding to a *Smarca1*-null mouse that we have previously characterized [1].

Conclusions Our results support an epigenetic mechanism in which *Iswi*-mediated histone variant exchange modulates *En1* expression levels to subsequently control cerebellar morphogenesis.

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