

Cerebellar ‘transcriptome’ reveals cell-type and stage-specific expression during postnatal development and tumorigenesis

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Disorders of cerebellar development can result in neurological disease and cancer. The identity of transcription factors that may uniquely mark and/or regulate development of single cerebellar cell types, however, is poorly understood. We used a library of ~1100 probes for expression of transcription factor (TF)-encoding genes (>70% of the mammalian ‘transcriptome’) to identify 227 genes with expression in developing neuronal and glial populations and 24 TFs that show cell-type- and stage-specific expression in granule cells, Purkinje cells and interneurons during postnatal cerebellar development. The utility of this panel is exemplified by analysis of medulloblastoma that shows upregulation of markers specific for early granule cell lineage, but not for other neuronal cell types, indicative of a unipotent precursor as well as a block in granule cell differentiation within the tumor. We propose that this atlas of the cerebellar transcriptome and the panel of 24 validated markers will be generally useful in analyses of mutations affecting postnatal cerebellar development and neoplasia.

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Introduction

The cerebellum is a midbrain–hindbrain derivative that participates in coordination of motor function as well as higher cognitive functions. Disorders of cerebellar development are implicated in neurological diseases, such as autism and medulloblastoma, a tumor primarily affecting children. Although the morphology of the cerebellar cortex has been extensively studied since the early 1900s (Cajal, 1911), the molecular mechanisms that

regulate proliferation and cell fate specification of its three main neuronal cell types remain obscure.

The distinctive layered organization of the cerebellar cortex facilitates identification of neuronal subpopulations. Proliferation of granule cell precursors occurs within the external granule cell layer (EGL)—a transient primordium beneath the pia mater. Once differentiated, glutamatergic granule cells receive signals from mossy fibers and convey them to Purkinje neurons (Altmann and Bayer, 1997). Those Purkinje neurons, in turn, are GABAergic and represent the only efferent relay from the cortex to the deep cerebellar nuclei and hence to the structures outside the cerebellum. They arise from the ventricular zone and migrate outward postmitotically to reach their final position between the molecular layer and the internal granule cell layer (IGL). Interneurons, that facilitate communication between granule cells and Purkinje neurons, also migrate outward from the ventricular zone, but continue to divide while in transit (Zhang and Goldman, 1996). Such basket/stellate cells and Golgi neurons settle in the molecular layer and IGL, respectively.

The main glial compartments within the cerebellum are oligodendrocytes and Bergmann glia. The latter can be found in close neighborhood to Purkinje cells. Bergmann glia cells send processes into the molecular layer that – among other functions – serve as guidance structures for migrating granule cells (Altmann and Bayer, 1997). Oligodendrocytes are mostly settled in the white matter. Apart from functions in myelin formation, they have recently been identified to play important roles in cerebellar cytoarchitecture in general and interneuron differentiation in particular (Mathis et al., 2003).

Transcription factors (TFs) play pivotal roles in the acquisition of cellular identity and maturation into specialized neuronal and glial cell types. TFs with known roles in development of cerebellar EGL precursors include *Atoh1* and *Nmyc1* (Ben Arie et al., 1997; Kenney et al., 2003). Later stages of granule cell development require *Zic1* and *Neurod1* (Aruga et al., 1998; Miyata et al., 1999). However, many aspects of transcriptional regulation during cerebellar development remain to be elucidated. For instance, almost nothing is known about the molecular pathways controlling the maturation of inhibitory interneurons.

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Table 1
Transcriptional factors expressed in the cerebellum

Gene Name	Domain	Gene ID	P7				P15				P22				DCN	Glia
			EGL	PK	IGL	WM	ML	PK	IGL	WM	ML	PK	IGL	WM		
Alf1	bHLH	21406	+	+	-	+	-	+	-	-	-	-	-	-	-	+
Ankhzn	ZN btb/poz	11736	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Arix	homeobox	11859	+	+	+	-	-	+	+	-	-	+	+	-	-	-
ARNT	bHLH	11863	+	-	+	-	-	-	+	-	-	-	+	-	-	-
ARNT2	bHLH	11864	+	+	-	-	-	-	-	-	-	-	-	-	+	-
ARNTL	bHLH	11865	-	+	-	-	-	-	-	-	-	-	-	-	-	-
Atf1	bZIP	11908	-	+	-	-	-	+	-	-	-	-	-	-	-	-
Atf4	bZIP	11911	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Barhl1	homeobox	54422	+	-	+	-	-	-	+	-	-	-	-	-	-	-
Bcl6	ZN btb/poz	12053	-	-	-	-	-	-	+	-	-	-	+	-	-	-
Bhlhb5	bHLH	59058	+	+	-	-	+	-	-	-	+	-	-	-	-	-
Bmi1 ^a	ZN RING	12151	+	-	+	-	-	-	+	-	-	-	+	-	-	-
Brd2	bromo	14312	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Brd4	bromo	57261	+	-	+	-	-	-	+	-	-	-	-	-	-	-
CFOS	bZIP	14281	-	-	-	-	-	-	-	-	-	+	-	-	-	-
CHES1	Forkhead	71375	-	-	+	-	-	-	+	-	-	-	+	-	-	-
Cited2	cited	17684	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Creb3	bZIP	12913	-	-	+	-	-	-	-	-	-	-	-	-	-	-
Crebl1	bZIP	12915	-	-	+	-	-	+	-	-	-	-	-	-	-	-
Csrp2	lim	13008	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Cux2	homeobox	13048	-	+	-	-	-	+	-	+	-	+	-	+	-	-
DIWS1T	GTF2I	14886	+	+	+	-	-	+	-	-	-	-	-	-	-	-
Dmbx1	homeobox	140477	-	-	+	-	-	-	-	-	-	-	-	-	+	-
E02	homeobox	15242	+	+	-	-	-	+	+	-	-	+	+	-	-	-
E2f1	e2f	13555	+	-	-	-	-	-	-	-	-	-	-	-	-	-
E2f2	e2f	242705	+	-	-	-	-	-	-	-	-	-	-	-	-	-
E2f3	e2f	13557	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Ebf	bHLH	13591	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Edr1	polycomb	13619	-	+	+	+	-	+	+	+	-	+	+	+	-	-
Egr4	ZN C2H2	13656	-	-	+	-	-	-	+	-	-	-	+	-	-	-
Elf1	ETS	13709	+	-	+	-	-	-	+	-	-	-	+	-	-	-
Elf2	ETS	69257	+	-	-	-	-	-	-	-	-	-	-	-	-	-
ELK1P	ETS	13712	+	-	+	-	-	-	+	-	-	-	+	-	-	-
En1	homeobox	13798	+	-	+	-	-	-	+	-	-	-	-	-	-	-
En2 ^b	homeobox	13799	+	-	+	-	-	-	+	-	+	-	+	-	-	-
Erf	ETS	13875	-	-	-	+	-	-	-	+	-	-	-	+	-	-
Esr1	nurec	13982	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Esg	nurec	26381	-	-	+	-	+	-	+	-	+	-	+	-	+	-
ETS1	ETS	23871	+	+	+	+	+	+	+	+	+	+	+	+	-	-
ETS2	ETS	23872	+	-	-	-	-	-	+	-	-	-	+	-	-	-
Etv1	ETS	14009	+	-	+	-	-	+	-	-	-	+	-	-	-	-
Etv6	ETS	14011	-	-	-	+	-	-	-	+	-	-	-	+	-	-
Evx2	homeobox	14029	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Fhl2	lim	14200	-	-	-	-	-	-	-	-	-	-	-	-	-	+
FoxA1	Forkhead	15375	-	-	-	-	-	-	-	-	-	-	-	-	+	-
FoxA2	Forkhead	15376	-	-	-	-	-	-	-	-	-	-	-	-	+	-
FoxD4	Forkhead	14237	-	-	-	-	-	-	-	-	-	-	-	-	+	-
FoxL4	Forkhead	14241	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Foxm1	Forkhead	14235	+	-	-	-	-	-	-	-	-	-	-	-	-	-
FoxO6	Forkhead	329934	+	+	+	-	-	+	+	-	-	+	+	-	-	-
Foxp2	Forkhead	114142	-	+	-	-	-	+	-	-	-	-	-	-	-	-
Foxp4	Forkhead	74123	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Gabpa	ETS	14390	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Gbx2	homeobox	14472	-	-	-	-	-	-	-	-	-	-	-	-	+	-
Gli1	ZN C2H2	14632	+	+	-	-	-	+	-	-	-	+	-	-	-	-
Gli2	ZN C2H2	14633	+	-	-	-	-	-	+	-	-	-	+	-	-	-
Gli3	ZN C2H2	14634	+	+	+	-	-	+	+	-	-	+	+	-	-	-
Gliz	bZIP	14605	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Hes1	homeobox	15205	-	+	+	-	-	+	+	-	-	-	+	-	-	-
Hes3 ^c	bHLH	15207	-	+	-	-	-	+	-	-	-	+	-	-	-	-
Hes5	bHLH	15208	-	-	+	-	-	-	+	-	-	-	+	-	-	-

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