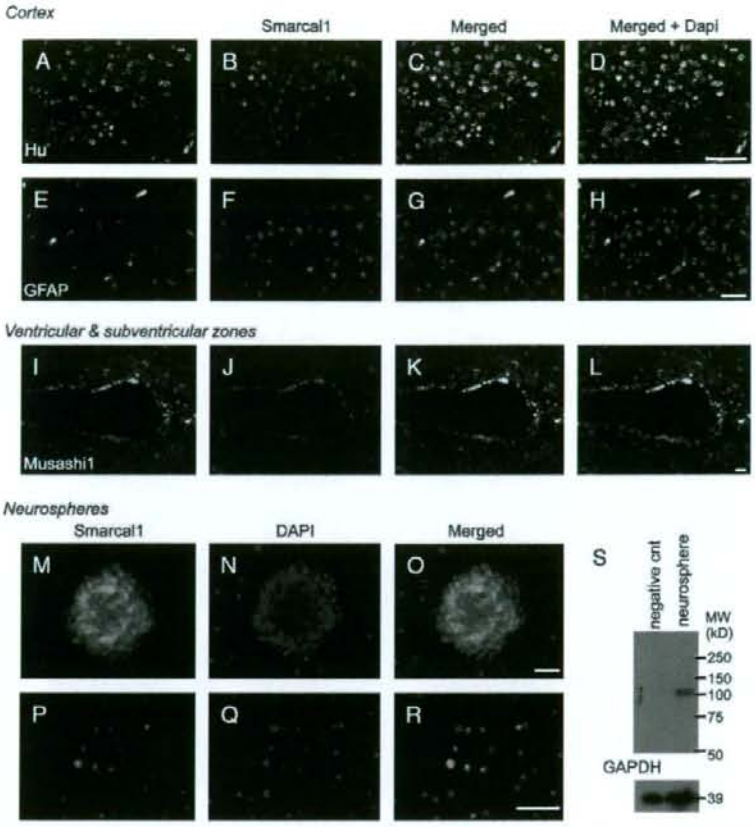


**FIGURE 3.** Immunofluorescent characterization of Smarcal1 expression in an adult mouse brain. Smarcal1 colocalizes with Hu **(A–D)** but not with glial fibrillary acidic protein **(E–H)** in the cortex, and with Musashi1 in the ventricular zone and subventricular zone **(I–L)**. As detected by immunofluorescence **(M–R)** and Western blot **(S)**, Smarcal1 is also expressed in cultured neurospheres **(M–O)** and in the individual cells dissociated from the neurospheres **(P–R)**. The negative control for the Western blot is an extract from lymphoblastoid cells from a patient homozygous for deletion of the *SMARCAL1* gene promoter and first 4 exons. Bar = 50 μm. cnt, control; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

expression of SMARCAL1 during brain development suggest that deficiency of SMARCAL1 may cause defective neurodevelopment. To investigate this possibility, we examined available microscopic sections of brain tissue on Patient SD60, who died of cardiopulmonary arrest at the age of 13 years (10), and Patient SD 84, who died of pulmonary hypertension and right heart failure at the age of 23 years (21). Both had had a head circumference of less than the third percentile and normal language, social, motor, and cognitive development. They had excelled academically, as is usual for SIOD patients prior to the onset of cerebral ischemic attacks, and they did not have a seizure disorder. The neuropathologic examination in these cases is regrettably incomplete. Vascular pathology was observed and was previously reported based on our initial observations of several microscopic slides that were available from autopsy material (10). Upon request, additional microscopic slides and some paraffin blocks were kindly sent to us by referring institutions; however, not all regions were sampled or identified. Despite these limitations, we studied the available materials and report our interpretations for comparison to more complete analyses.

Because of the limited samples available, the following observations cannot be considered conclusive or complete. Rather, they are to serve as a basis for future studies. According to the autopsy reports, the brains of Patients SD60 and SD84 weighed less than normal and had areas of infarction and ischemia (Table 2). Despite normal CNS function and antemortem brain magnetic resonance imaging, the nonischemic areas of both brains had very subtle, but consistent, histologic abnormalities. In several focal regions of cerebellar folia, the Purkinje cells (as defined by serial sectioning) seemed to be poorly aligned (Supplemental Fig. 2A); however, because of incomplete materials, the vermis, which has been reported as abnormal by magnetic resonance imaging in some SIOD patients (29), could not be assessed. In the cerebral cortex and the subcortical white matter, focal structural anomalies were observed in 50% of the available cortical sections. The microscopic

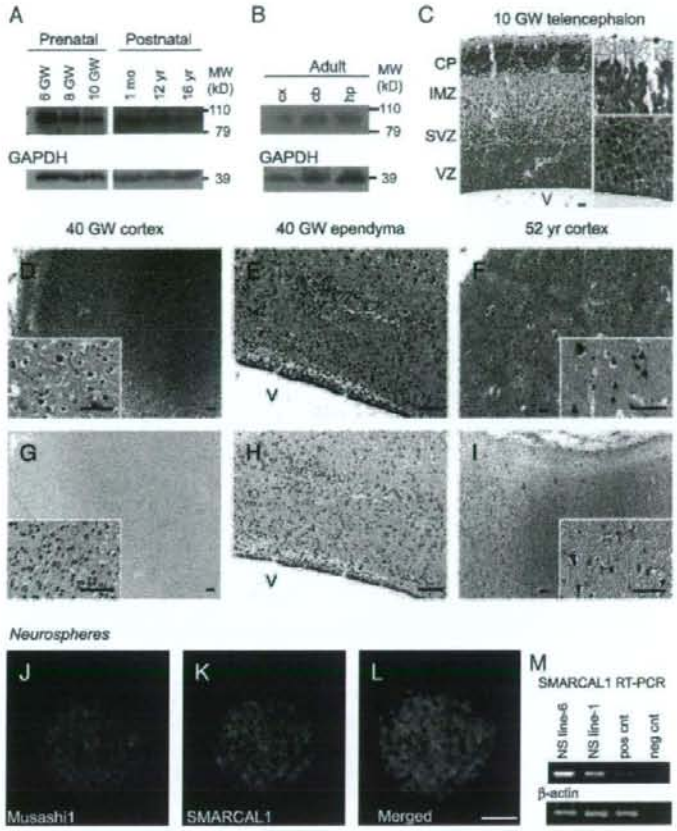


**FIGURE 4.** Western blot and immunohistochemical analyses of SMARCAL1 protein expression in the human brain. **(A)** Western analysis for SMARCAL1 expression in protein extracts from whole human brain at 6, 8, and 10 gestational weeks (GW); the brain is predominantly neural precursors at 6 weeks of gestation. The membrane was concurrently probed for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression to control for protein integrity and loading. **(B)** Western analysis for SMARCAL1 expression in protein extracts from the cortex (cx), cerebellum (cb), and hippocampus (hp) of the adult human brain. The membrane was concurrently probed for GAPDH expression to control for protein integrity and loading. **(C)** SMARCAL1 expression in the cerebrum of a human 10-GW brain. Cells in the ventricular zone (VZ), subventricular zone (SVZ), IMZ, and the CP express SMARCAL1. Higher-magnification image of SMARCAL1 expression in the CP of the human 10-GW brain (upper inset). Higher-magnification image of SMARCAL1 expression in the VZ and SVZ of the human 10-GW brain (lower inset). **(D, E)** Expression of SMARCAL1 in the cortex and ependyma of a 40-GW brain. The inset **(D)** shows SMARCAL1 expression in cortical Layer II. **(F)** Expression of SMARCAL1 in adult cortical neurons. The inset shows SMARCAL1 expression in cortical Layer II. **(G–I)** Serial sections treated with preimmune serum. As detected by immunofluorescence **(J–L)** and reverse-transcriptase-polymerase chain reaction **(M)**, SMARCAL1 is also expressed in cultured neurospheres. Bar = 50 μm. cnt, control; CP, cortical plate; IMZ, intermediate zone; V, ventricle.

malformations included subcortical "heterotopias," some of which were verified by serial sectioning to be separate from the cortex and not related to tangential sectioning (Supplemental Fig. 2B). Upon serial sectioning, some of the heterotopias (Supplemental Fig. 2B; marked with a star) represented an extension of the "expanded cortex" as described in the succeeding sentences. Within these areas, no organization of neurons could be discerned. There were also isolated sections of expanded cortex. For example, the cortical thickness in temporal cortex of SD84 ranged from 2.0 to 6.0 mm, whereas in an age-matched control, the same regions measured 1.5 to 4.5 mm. In the "thicker" regions of cortex, there were usually several other associated findings. There was a loss of a well-defined Layer II in each section examined (Supplemental Fig. 2C) as defined by calbindin immunoreactivity, which is normally present in only Layer II neurons (control frontal cortex; Supplemental Fig. 2D). There was poor definition of the cortical gray-white matter junction similar to that observed in cortical dysplasia. In addition, near the expanded cortex, serial sections frequently revealed a failure of separation of gyri and aberrant definition of sulci (data not shown). Importantly, the malformations were

**TABLE 2.** Summary of Brain Pathologic Findings in SIOD Patients SD60 and SD84

| | SIOD Patient | |
|---|---|---|
| | **SD60** | **SD84** |
| Gross pathology | | |
| Brain weight | 1,100 g (normal, 1,300 g) | 1,020 g (normal, 1,300–1,400 g) |
| Blood vessels* | Abnormal | Abnormal |
| Cerebrum | Normal gross structure, diffuse ischemic changes | Normal gross structure, recent and old focal infarcts |
| Cerebellum | Normal gross appearance, possible focal Purkinje cell crowding | Normal gross appearance, possible focal Purkinje cell crowding |
| Brainstem | Normal | Normal |
| Cortical pathology | | |
| Focal cortical expansion | 4/9† | 10/24† |
| Subcortical heterotopia | 1/9† | 4/24† |
| Incomplete sulcation | 3/9† | 5/24† |
| Displaced Layer II | 2/2‡ | 3/3‡ |

*, The blood vessel pathology is described in Reference 10.
†, The denominator is the number of cortical sections available, and the numerator is the number of these sections with the observed alteration.
‡, The denominator is the number of cortical sections stained with anti-calbindin, and the numerator is the number of these sections with the abnormal localization of calbindin-positive neurons.
SIOD, Schimke immuno-osseous dysplasia.

microscopic and required serial sectioning to assess their positions within the cortex. Probably only a powerful and detailed imaging system could have identified them in the living patient.

Because of the role of SMARCAL1 in cell proliferation and its presence in neural precursor cells (and because of the findings in the SIOD cases), we questioned whether neural precursor cells can be identified in subventricular regions in the brain tissue samples. Using the markers Mushashi-1 and Nestin (30), we detected neural precursor cells, indicating that there was not a complete absence of these neural precursor cells in these small brains (Supplemental Figs. 3A–L). There were, however, fewer of them than in the control brain sample (Supplemental Fig. 3P).

### Knockdown Studies in Mouse Neurospheres

Based on the suggestion that deficiency of SMARCAL1 contributes to a reduced number of precursors, we performed siRNA knockdown of Smarcal1 in mouse neurospheres. The results indicated that the neurospheres grow less well when they were made deficient in Smarcal1 (Supplemental Figs. 3Q–U). Using 2 different siRNA oligonucleotides for Smarcal1 neurospheres derived from ICR and 129 SvEv mice, 3 independent experiments for each condition showed 53% to 67% transfection efficiency and, as measured by Western blot, a 40% to 50% knockdown of SMARCAL1 protein 4 days after transfection (Supplemental Fig. 3V). Four days after transfection with the Smarcal1 siRNA, the number and radii of neurospheres as well as the number of cells per neurosphere were significantly reduced ($p < 0.001$), whereas cells transfected with the control siRNA were unaffected (Supplemental Figs. 3Q–U). Therefore, although deficiency for SMARCAL1 does not cause a complete loss of neural precursors, it may be one factor contributing to the small brain size in these patients. These results require confirmation both when there are additional studies on SIOD patient tissues and when *Smarcal1* knockout mice become available.

## DISCUSSION

SMARCAL1 is a unique member of the SNF2 family of chromatin remodeling proteins that have DNA-dependent adenosine triphosphatase activity (12, 31). We recently determined that mutations of SMARCAL1 cause SIOD (9). In this report, we show for the first time that 1) there is expression of SMARCAL1 in CNS neurons and neural precursors in both humans and mice; 2) SIOD patients often have a reduced head circumference (microcephaly); and 3) autopsy observations of 2 male SIOD patients identify subtle histologic features suggestive of perturbed neuron-glial migration that warrant confirmation and detailed examination in future autopsy studies of SIOD.

The microcephaly is consistent with our previous hypothesis that SMARCAL1 expression facilitates cellular proliferation (9, 10, 19). The head circumference measurements were obtained at birth or prior to the onset of cerebral ischemia, which contributes to reduced brain weight and the acquired cerebellar atrophy reported in some SIOD patients (29). Surprisingly, the microcephaly did not correlate with other clinical features, and despite microcephaly and the subtle histologic features suggestive of perturbed neuron-glial migration, most SIOD patients had generally normal social, language, motor, and cognitive development, and very few had seizures (Table 1). These observations suggest that SMARCAL1 participates in the modulation of both neural proliferation and differentiation but that the morphologic abnormalities that result from deficiency of SMARCAL1 rarely cause serious neurophysiologic dysfunction or developmental deficits. Examination of the brains from SIOD patients who manifest abnormal development or seizures would, however, clarify the range of CNS abnormalities associated with SMARCAL1 deficiency.

The lack of overt functional CNS deficits in most SIOD patients contrasts with the severe neurologic deficits observed with deficiency of the SNF2 factor α-thalassemia mental retardation, X-linked syndrome (32). Individuals with primary microcephaly may, however, have minimal neurologic problems (33–35). Unlike many other skeletal dysplasias and genetic disorders of generalized growth, the relationship between stature and head circumference is not uniform in SIOD. This suggests that loss of SMARCAL1 function is not sufficient for the development of microcephaly, and that stochastic, epigenetic, environmental, or other genetic factors might also contribute to the microcephaly in SIOD patients.

Poor brain growth can result from a reduction in cell number or size but generally has been ascribed to a reduction in cell number (36). Such a reduction can arise either from reduced proliferation or from increased death of glia and/or neurons (37). Based on the spatio-temporal expression of SMARCAL1/Smarcal1 in the human brain, SMARCAL1 deficiency might affect neural precursor viability from early in embryogenesis to postnatal life, thereby contributing to the decreased mean prenatal and postnatal head circumferences observed in many of the patients with SIOD. Moreover, the early-onset cognitive impairment that we have observed in some adult SIOD patients might be attributable to a failure of ongoing neurogenesis in addition to the cerebrovascular disease that results in stroke-like episodes (10, 29, 38, 39).

In addition to the modulation of numbers of neural precursor cells, our findings also implicate SMARCAL1 in the regulation of neuronal migration and cortical differentiation. The presence of microscopic periventricular heterotopia, cortical microdysgenesis, and aberrant gyration seen in both autopsy cases have been observed in other disorders of neural migration and cortical patterning (40). Cortical microdysgenesis has been associated with infantile spasms (41), primary generalized epilepsy (42), partial epilepsy (43), dyslexia (44, 45), congenital mental retardation (46), and autism-like disorders (46). Although neither of the autopsy cases we studied was associated with these disorders, histories of the clinical cohort did reveal some of these conditions: 2 SIOD patients had seizures, 7 had EEG changes, and there was mild mental delay in 7. These clinical features in SIOD patients warrant careful examination for evidence of histologic correlates that may suggest perturbed neuron-glial migration. It might also be worth considering whether SIOD patients, who have generally intractable migraine-like headaches, might also be manifesting a partial seizure disorder (16, 47).

The histologic features suggestive of perturbed neuron-glial migration identified would arise from a disturbance in the later stages of radial neuronal migration and cortical organization, whereas heterotopias would arise as a disturbance of the earlier stages of radial neuronal migration. The molecular basis of the cortical microdysgenesis in neurologic disorders is undefined, although some have suggested aberrant secretion of reelin by Cajal-Retzius neurons (48). We found expression of SMARCAL1 in the migrating neuronal precursors, cortical neurons, and in the Cajal-Retzius neurons, but not in cortical oligodendrocytes or astrocytes (Fig. 5). Based on our prior studies suggesting a cell-autonomous function for SMARCAL1 (10, 49, 50), we

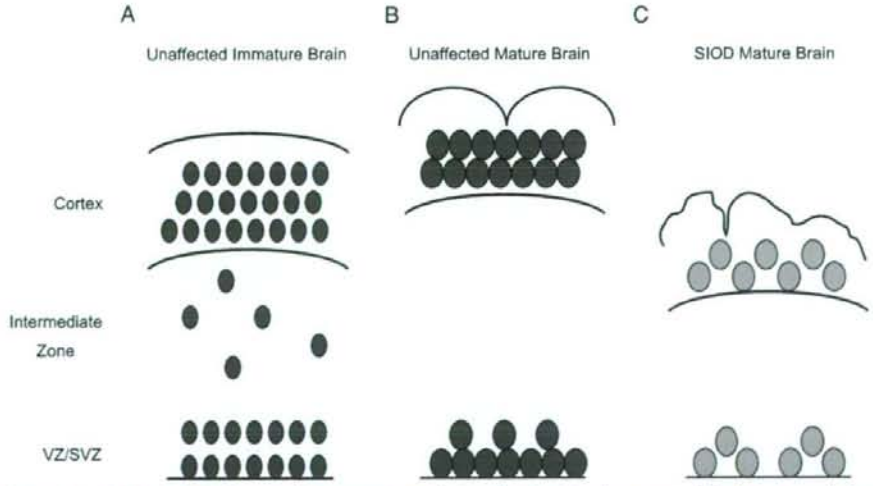


**FIGURE 5.** Schematic of SMARCAL1/Smarcal1 expression during brain development. **(A)** In normal developing brain, SMARCAL1 is present in cells of neuronal lineage, including neural precursor cells, migrating immature neurons, and postmigrating neurons in cortex. **(B)** SMARCAL1 expression remains both in the adult neural stem cells in ventricular zone/subventricular zone and mature cortical neurons. **(C)** When SMARCAL1 is deficient, the brain is smaller than normal, possibly because the numbers of adult stem cells may be reduced. Potential impairment in neuronal migration and cortical differentiation can result in histologic features suggestive of lesions such as microdysgenesis and abnormal cortical layering.

hypothesize that the cortical malformations can arise as a consequence of SMARCAL1 dysfunction within the neuronal lineage.

As a member of the swi/snf class of enzymes, SMARCAL1 might alter chromatin structure and/or expression of genes necessary for neural precursor viability or proliferation as well as for effective neuronal migration. Involvement of chromatin remodeling factors in neural precursor renewal has been observed for the mammalian Polycomb group enzyme Bmi-1 (51, 52) and for the Brm-/Brg-1-associated complexes (53–55). Brm-/Brg-1-associated complexes also modulate glial and neuronal differentiation. The murine SWI/SNF (BAF) subunits have nonredundant and dosage-sensitive roles in neural development. Indeed, mice heterozygous for either Brg or BAF155/Srg3 are predisposed to exencephaly (54, 55), and Brg is essential for the repression of neuronal commitment in neural stem cells (56). Furthermore, the transition from proliferating neural stem/progenitor cells to postmitotic neurons requires a switch in subunit composition of the Brm-/Brg-1-associated complexes (53). We postulate that SMARCAL1/Smarcal1 might be a member of other chromatin remodeling complexes that similarly regulate the expression of genes necessary for neural precursor viability and/or renewal as well as for neuronal migration and cortical differentiation. Thus, deficiency of SMARCAL1 would result in a paucity of neural precursors, abnormalities of neuronal migration, and cortical malformations.

A role for SMARCAL1/Smarcal1 in modulating precursor cell renewal and differentiation can also explain the hematopoiesis defects observed in some SIOD patients (9, 10). If SMARCAL1 promotes viability by inhibiting apoptosis of bone marrow stem cells and influences their differentiation along various lineages, this might explain the stem cell factor-resistant bone marrow failure and the high prevalence of T-cell immunodeficiency among SIOD patients (9).

In summary, we have shown for the first time that the disruption of SMARCAL1 expression in patients with SIOD can result in a small brain size, minimal cortical dysgenesis, and other subtle histologic features suggestive of perturbed neuron-glial migration that are often not detected by clinical and magnetic resonance imaging studies. In view of its similarity to other chromatin remodeling proteins, we propose that SMARCAL1 might act as a chromatin chaperone and thereby modulate the expression of a subset of genes involved in neural development.

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