SMARCB1

SMARCB1 (also known as SNF5, INI1, or BAF47) is a protein that plays an important role in the regulation of gene expression and chromatin remodeling. It is a subunit of the SWI/SNF chromatin-remodeling complex, which uses the energy from ATP hydrolysis to alter the structure of chromatin and regulate gene transcription.

SMARCB1 acts as a tumor suppressor gene and mutations in this gene have been linked to the development of a rare type of cancer called a malignant rhabdoid tumor (MRT). MRTs are aggressive tumors that typically occur in young children and are associated with a poor prognosis. Loss of SMARCB1 function is also seen in other types of cancer, including some cases of renal cell carcinoma and atypical teratoid/rhabdoid tumor.

The exact mechanisms by which loss of SMARCB1 contributes to tumor development are not fully understood, but it is thought to involve the deregulation of gene expression and disruption of normal cellular processes. SMARCB1 is also involved in the regulation of cell growth and differentiation, and its loss can lead to abnormal proliferation and differentiation of cells.

The diagnosis of MRT often involves genetic testing for mutations in the SMARCB1 gene, and treatment typically involves a combination of surgery, chemotherapy, and radiation therapy. There is ongoing research into the mechanisms of SMARCB1 function and the development of targeted therapies for SMARCB1-associated tumors.

SMARCB1 encodes a subunit of the SWI/SNF complex involved in chromatin remodeling. Pathogenic variants (PV) in this gene can give rise to three conditions. Heterozygous loss-of-function germline PV cause rhabdoid tumor predisposition syndrome and schwannomatosis. Missense PV and small in-frame deletions in exons 8 and 9 result in Coffin-Siris syndrome, which is characterized by intellectual disability (ID), coarse facial features, and fifth digit anomalies.

By a gene matching approach, individuals with a similar SMARCB1 PV were identified. Informed consent was obtained and patient data were collected to further establish genotype-phenotype relationship.

A recurrent de novo missense PV (c.110G>A;p.Arg37His) in exon 2 of SMARCB1, encoding the DNA-binding domain, was identified in four individuals from different genetic centers. They shared a distinct phenotype consisting of profound ID and hydrocephalus due to choroid plexus hyperplasia. Other shared features include severe neonatal feeding difficulties; congenital heart, kidney, and eye anomalies; obstructive sleep apnea; and anemia.

The p.Arg37His PV in the DNA-binding domain of SMARCB1 causes a distinctive syndrome, likely through a gain-of-function or dominant-negative effect, which is characterized by severe ID and hydrocephalus resulting from choroid plexus hyperplasia. This report broadens the phenotypic spectrum associated with PV in SMARCB1 [1)].

The protein encoded by this gene is part of a complex that relieves repressive chromatin structures, allowing the transcriptional machinery to access its targets more effectively. The encoded nuclear

protein may also bind to and enhance the DNA joining activity of HIV-1 integrase. This gene has been found to be a tumor suppressor, and mutations in it have been associated with malignant rhabdoid tumors. Two transcript variants encoding different isoforms have been found for this gene.

Loss of SMARCB1/INI1 expression is considered to be a hallmark for childhood chordomas (CCs). Although mutation/loss of 22q has strongly established the loss of SMARCB1/INI1 in cancers, the cause in CCs remains elusive. Recent studies suggest role of MicroRNAs in regulation of SMARCB1/INI1 expressions.

Malgulwar et al. examined 5 reported/target predicted MicroRNAs to SMARCB1/INI1 in SMARCB1/INI1 immunonegative and immunopositive cases, and found upregulation of miR-671-5p and miR-193a-5p in SMARCB1/INI1-immunonegative cases. Notably, these two MicroRNAs were significantly predicted to target TGF-β signaling, suggestive of dysregulation of developmental and osteoblast regulation pathway in CCs. Overall, we suggest miR-671-5p- and miR-193a-5p-mediated epigenetic mode of SMARCB1/INI1 loss and downregulated TGF-β pathway in CCs [2].

see SMARCB1 in Atypical teratoid rhabdoid tumor.

Malignant rhabdoid tumors (MRT), a pediatric cancer that most frequently appears in the kidney and brain, generally lack SNF5 (SMARCB1/INI1), a subunit of the SWI/SNF chromatin-remodeling complex.

A study aimed to characterize SNF5 expression and investigate the relationship between SNF5 and clinicopathological features in skull base chordoma. 48 patients diagnosed with skull base chordoma were enrolled in this study. Tissue microarray and immunohistochemistry were performed to evaluate the expression of SNF5 in skull base chordoma. Kaplan-Meier survival analysis was used to assess survival. Multivariable Cox regression analysis was used to identify risk factors affecting patient survival. The H-scores for cytoplasmic SNF5 ranged from 124.47 to 254.52. Low expression of SNF5 was correlated with shorter overall survival (OS) ($p = 0.021$). Patients with age > 55 years old had shorter progression free survival (PFS) and OS times than patients whose age ≤ 55 years old ($p = 0.005$ and 0.003, respectively). The gross total resection group showed longer PFS than the non-gross total resection group ($p = 0.024$). Females showed shorter PFS times than males ($p = 0.033$). Multivariable Cox regression analysis showed that age, extent of resection and sex were independent prognostic factors for PFS ($p = 0.010$, 0.013 and 0.042, respectively). Age was an independent prognostic factor for OS ($p = 0.010$). Our study indicate that low expression of SNF5 is associated with poor prognosis in skull base chordoma [3].

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3)
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