SMARCA4 gene

SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4

Normal Function

The *SMARCA4* gene provides instructions for making a protein called BRG1, which forms one piece (subunit) of several different protein groupings called SWI/SNF protein complexes. SWI/SNF complexes regulate gene activity (expression) by a process known as chromatin remodeling. Chromatin is the network of DNA and protein that packages DNA into chromosomes. The structure of chromatin can be changed (remodeled) to alter how tightly DNA is packaged. Chromatin remodeling is one way gene expression is regulated during development; when DNA is tightly packed, gene expression is lower than when DNA is loosely packed. The BRG1 protein uses a molecule called ATP to provide energy for chromatin remodeling, although the protein's specific role in remodeling is unclear.

Through their ability to regulate gene activity, SWI/SNF complexes are involved in many processes, including repairing damaged DNA; copying (replicating) DNA; and controlling the growth, division, and maturation (differentiation) of cells. Through these processes, the BRG1 protein and other SWI/SNF subunits are thought to act as tumor suppressors, which keep cells from growing and dividing too rapidly or in an uncontrolled way.

Health Conditions Related to Genetic Changes

Coffin-Siris syndrome

At least 16 mutations in the *SMARCA4* gene can cause Coffin-Siris syndrome. This condition is characterized by delayed development, abnormalities of the fifth (pinky) fingers or toes, and characteristic facial features that are described as coarse. The *SMARCA4* gene mutations involved in Coffin-Siris syndrome are germline mutations, which means that they are present in cells throughout the body. The mutations change single protein building blocks (amino acids) in or remove an amino acid from the BRG1 protein. Although it is unclear how these changes affect SWI/SNF complexes, researchers suggest that *SMARCA4* gene mutations result in abnormal chromatin remodeling. Disturbance of this process alters the activity of many genes and disrupts several cellular processes, which could explain the diverse signs and symptoms of Coffin-Siris syndrome. People with Coffin-Siris syndrome do not appear to have an increased risk of cancer (see below).

Rhabdoid tumor predisposition syndrome

At least six germline mutations in the *SMARCA4* gene have been identified in people with rhabdoid tumor predisposition syndrome (RTPS). RTPS is characterized by a high risk of developing cancerous (malignant) growths called rhabdoid tumors. These tumors most often occur in the brain and spinal cord (central nervous system) or in the kidney, but they can occur in other organs and tissues of the body. Some affected children also develop noncancerous (benign) tumors called schwannomas, which grow on nerves. Women with RTPS are at increased risk of developing a rare type of ovarian cancer called small cell cancer of the ovary, hypercalcemic type (SCCOHT).

In addition to the germline mutation affecting one copy of the *SMARCA4* gene in each cell, an additional genetic change that deletes the normal copy of the gene is needed for a tumor to develop. This additional change is present only in the cancerous cells. Such changes are known as somatic mutations. In combination, the germline and somatic mutations lead to the absence of BRG1 protein. This absence likely impairs the tumor suppressor functions of the protein, but the specific mechanism that leads to rhabdoid tumors is unknown.

Lung cancer

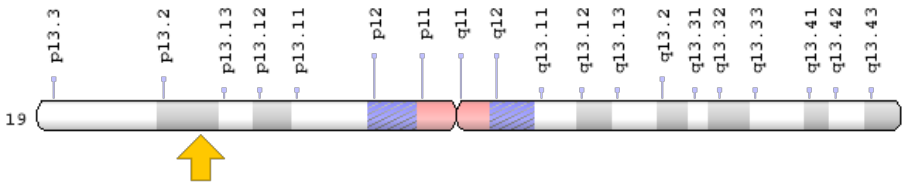
Other cancers

Somatic mutations in both copies of the *SMARCA4* gene, which result in the absence of SMARCA4 protein, cause noninherited (sporadic) rhabdoid tumors in children. Somatic mutations in the *SMARCA4* gene have also been found in certain other types of cancer, particularly lung cancer and other cancers in the chest called *SMARCA4*-deficiency thoracic sarcomas. The mechanism by which mutations in the *SMARCA4* gene contribute to these tumors is unknown, although it is thought that changes in SWI/SNF complexes are involved. These changes may impair normal cell differentiation, which leads to the overgrowth of certain cell types, causing cancer. Alternatively, abnormal SWI/SNF complexes may disrupt the regulation of genes that help control the growth and division of cells, which leads to cancer. It is likely that other genetic changes in addition to *SMARCA4* gene mutations are necessary for cancer development.

Chromosomal Location

Cytogenetic Location: 19p13.2, which is the short (p) arm of chromosome 19 at position 13.2

Molecular Location: base pairs 10,960,922 to 11,062,282 on chromosome 19 (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ATP-dependent helicase SMARCA4
- BAF190
- BAF190A
- brahma protein-like 1
- BRG1
- BRG1-associated factor 190A
- BRM/SWI2-related gene 1
- FLJ39786
- hSNF2b
- MRD16
- nuclear protein GRB1
- protein brahma homolog 1
- protein BRG-1
- RTPS2
- SMCA4_HUMAN
- SNF2
- SNF2-beta
- SNF2-like 4
- SNF2L4

- SNF2LB
- sucrose nonfermenting-like 4
- SWI2
- transcription activator BRG1

Additional Information & Resources

Educational Resources

- Molecular Biology of the Cell (fourth edition, 2002): ATP-Driven Chromatin Remodeling Machines Change Nucleosome Structure
  https://www.ncbi.nlm.nih.gov/books/NBK26834/#A644
- Molecular Biology of the Cell (fourth edition, 2002): Chromosomal DNA and Its Packaging in the Chromatin Fiber
  https://www.ncbi.nlm.nih.gov/books/NBK26834/

Clinical Information from GeneReviews

- Coffin-Siris Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK131811
- Rhabdoid Tumor Predisposition Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK469816

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28SMARCA4%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A, MEMBER 4
  http://omim.org/entry/603254

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/SMARCA4ID42333ch19p13.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=SMARCA4%5Bgene%5D
- HGNC Gene Symbol Report
  https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/HGNC:11100

- Monarch Initiative
  https://monarchinitiative.org/gene/NCBIGene:6597
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/6597
- UniProt
  https://www.uniprot.org/uniprot/P51532

Sources for This Summary

- Le Loarer F, Watson S, Pierron G, de Montpreville VT, Ballet S, Firmin N, Auguste A, Pissaloux D, Boyault S, Paindavoine S, Dechelotte PJ, Besse B, Vignaud JM, Brevet M, Fadel E, Richer W, Treilleux I, Masliah-Planchon J, Devouassoux-Shisheboran M, Zalcman G, Allory Y, Bourdeaut F, Thivolet-Bejui F, Ranchere-Vince D, Girard N, Lantuejoul S, Galateau-Sallé F, Coindre JM, Leary A, Delattre O, Blay JY, Tirode F. SMARCA4 inactivation defines a group of undifferentiated thoracic malignancies transcriptionally related to BAF-deficient sarcomas. Nat Genet. 2015 Oct;47(10): 1200-5. doi: 10.1038/ng.3399. Epub 2015 Sep 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26343384
- Medina PP, Sanchez-Cespedes M. Involvement of the chromatin-remodeling factor BRG1/SMARCA4 in human cancer. Epigenetics. 2008 Mar-Apr;3(2):64-8. Epub 2008 Apr 17. Review. Erratum in: Epigenetics. 2008 Jul-Aug;3(4):234. Cespedes, Montse Sanchez [corrected to Sanchez-Cespedes, Montse].
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18437052
- Rodriguez-Nieto S, Cañada A, Pros E, Pinto AI, Torres-Lanzas J, Lopez-Rios F, Sanchez-Verde L, Pisano DG, Sanchez-Cespedes M. Massive parallel DNA pyrosequencing analysis of the tumor suppressor BRG1/SMARCA4 in lung primary tumors. Hum Mutat. 2011 Feb;32(2):E1999-2017. doi: 10.1002/humu.21415. Epub 2010 Dec 7.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21280140
- OMIM: SWI/SNF-RELATED, MATRIX-ASSOCIATED, ACTIN-DEPENDENT REGULATOR OF CHROMATIN, SUBFAMILY A, MEMBER 4
  http://omim.org/entry/603254
- Schneppenheim R, Frühwald MC, Gesk S, Hasselblatt M, Jeibmann A, Kordes U, Kreuz M, Leuschner I, Martin Subero JI, Obser T, Oyen F, Vater I, Siebert R. Germline nonsense mutation and somatic inactivation of SMARCA4/BRG1 in a family with rhabdoid tumor predisposition syndrome. Am J Hum Genet. 2010 Feb 12;86(2):279-84. doi: 10.1016/j.ajhg.2010.01.013. Epub 2010 Feb 4.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20137775
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2820190/
- Sredni ST, Tomita T. Rhabdoid tumor predisposition syndrome. Pediatr Dev Pathol. 2015 Jan-Feb; 18(1):49-58. doi: 10.2350/14-07-1531-MISC.1. Epub 2014 Dec 10.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25494491

- Tsurusaki Y, Okamoto N, Ohashi H, Kosho T, Imai Y, Hibi-Ko Y, Kaname T, Naritomi K, Kawame H, Wakui K, Fukushima Y, Homma T, Kato M, Hiraki Y, Yamagata T, Yano S, Mizuno S, Sakazume S, Ishii T, Nagai T, Shiina M, Ogata K, Ohta T, Niikawa N, Miyatake S, Okada I, Mizuguchi T, Doi H, Saitsu H, Miyake N, Matsumoto N. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. Nat Genet. 2012 Mar 18;44(4):376-8. doi: 10.1038/ng.2219.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22426308
- Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer. 2011 Jun 9;11(7):481-92. doi: 10.1038/nrc3068. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/21654818

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/SMARCA4

Reviewed: May 2018
Published: May 14, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services