

## Gene Section

### Short Communication

# SASH1 (SAM and SH3 domain containing 1)

Klaus-Peter Janssen

Department of Surgery, Technische Universitaet Muenchen, Ismaninger Str 22, 81675 Munich, Germany (KPJ)

Published in Atlas Database: August 2013

Online updated version : <http://AtlasGeneticsOncology.org/Genes/SASH1ID43799ch6q24.html>  
DOI: 10.4267/2042/53531

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.  
© 2014 Atlas of Genetics and Cytogenetics in Oncology and Haematology

## Abstract

Review on SASH1, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

## Identity

**Other names:** SH3D6A, dJ323M4, dJ323M4.1

**HGNC (Hugo):** SASH1

**Location:** 6q24.3

## DNA/RNA

### Note

Entrez Gene: 23328 C, Ensembl: ENSG00000111961 C, UCSC: uc003qme.1 D, Vega:OTTHUMG00000015773.

### Description

SASH1: located on human chromosome 6.

Detailed gene locus: 6q24.3: 148593440-148873186 (forward strand).

ENSEMBL Database: Gene ID:  
ENSG00000111961.

### Transcription

20 Protein-coding transcribed Exons, 7700 bp transcript, encoding 1247 amino acid residues.

### Pseudogene

No known pseudogenes.

## Protein

### Note

Human SASH1 is comprised of 1247 amino acid residues, with a pI of 5.7, and a molecular mass of

137 kDa (please note that the apparent mass on denaturing SDS-PAGE is higher, roughly 170 kDa). SASH1 contains the following domains (from amino- to carboxyterminus): a predicted short coiled-coil stretch (CC), two predicted nuclear localisation signals (NLS1 and NLS2), a Src-homology-3 domain (SH3, aa 557 - aa 614), a first sterile alpha motif (SAM1, aa 633 - aa 697), a proline-rich sequence (PPP, aa 978 - aa 1059), and a second sterile alpha motif domain (SAM2, aa 1177 - aa 1241).

### Description

Human SASH1 was first described in 2003 as putative tumor suppressor in breast cancer, it encodes a protein with both cytosolic and nuclear localisation.

It lacks enzymatic activity, but, due to its multiple protein-protein interactions domains (SH3, SAM, poly-prolin stretches), it is likely to serve as a signal-adaptor module that integrates and coordinates other proteins, thereby acting as a negative/positive signal transduction node.

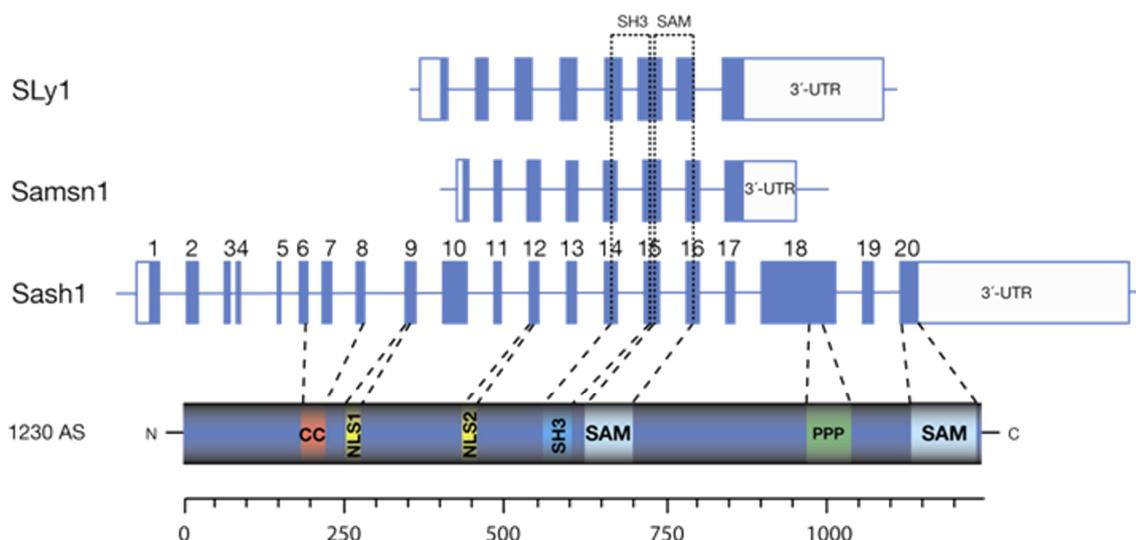
### Expression

SASH1 shows broad expression on protein level in human tissue and cell lines, as well as in mouse tissue.

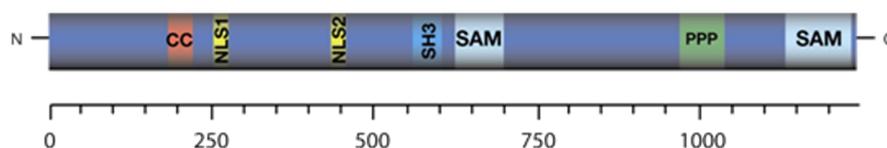
Exception: no or only weak expression has been found in lymphocytes.

### Localisation

SASH1 is found both in the cytosol, as well as in the nucleus, with the exception of the nucleolus. Enrichment in membrane-proximal areas in migrating cells at the lamellipodia (Martini et al., 2011).



**Schematic Structure of the Exon structure of human SASH1, as compared to the other members of the SLY-family of signal-adaptor proteins, SLy1 (SH3-protein expressed in lymphocytes), and SAMS1 (or SLy2).** At the bottom, the transcribed full-length protein is shown schematically. SASH1 is the largest member of the protein family, it is encoded by 20 exons. All SLY-family proteins share a central conserved NLS (nuclear localisation signal) sequence, a SH3 and a SAM domain (dotted line). SASH1 comprises, in addition, a coiled-coil (CC) motif, a N-terminally located NLS signal (NLS2), a poly-proline motif (PPP), and a second SAM domain at the C-terminus.



**Diagram schematically depicts human SASH1 protein (1247 aa), and the above-mentioned sequence-features:** coiled-coil stretch (CC), nuclear localisation signals (NLS1 and NLS2), Src-homology-3 domain (SH3), a sterile alpha motif (SAM), a proline-rich sequence (PPP).

## Function

SASH1 has no intrinsic enzyme activity, but can form multi-protein complexes due to its protein-protein interaction domains, and can modulate intracellular signal transduction. Moreover, SASH1 is implicated in the regulation of cell adhesion and migration (Martini et al., 2011).

## Homology

SASH1 belongs to the SLY-family, closest homologues: SLy1 and SLy2 (SH3-domain containing protein expressed in lymphocytes). Of note, SLy1 and SLy2 are much smaller (around 380 aa), and SLy1 is exclusively expressed in lymphocytes.

## Mutations

### Germinal

Heterozygous germline mutations have been identified in the three nonconsanguineous families with benign dermatologic features in a Chinese study (Zhou et al., 2013). However, no correlation

between these mutations and occurrence of malignoma has been reported so far:

- 1) T → G substitution at nucleotide 2126 (TAC → GAC) in exon 14, resulting in amino acid substitutions of Tyr to Asp (Y551D) at codon 551
- 2) T → C substitution at nucleotide 2019 (CTC → CCC) in exon 13, resulting in Leu to Pro at codon 515 (L515P)
- 3) G → A substitution (GAA → AAA) at position 2000 in exon 13, causing Glu to Lys at codon 509 (E509K).

### Somatic

No truncating or nonsense mutations have been identified in somatic cells for SASH1 in a study on human breast cancer (Zeller et al., 2003).

## Implicated in

### Breast cancer

#### Note

Loss of the gene-internal microsatellite DNA marker D6S311 was found in 30% of samples of

primary breast carcinoma, and the LOH was significantly correlated with poor survival and increase in tumor size. In established human mammary cancer cell lines, SASH1 is expressed at relatively low levels. SASH1 is downregulated in the majority (74%) of breast tumors in comparison with corresponding normal breast epithelia. In addition, SASH1 is also downregulated in tumors of the lung and thyroid. (Zeller et al., 2003).

### **Colorectal cancer**

#### **Note**

The mRNA as well as protein expression of SASH1 was strongly and significantly reduced in colon cancer of UICC stage II, III, and IV, as well as in colorectal liver metastases. In contrast, SASH1 expression was not significantly altered in benign adenomas and in early stage lesions (UICC I). Around 40% of primary colon tumours tested (n=113) showed a 10-fold or stronger reduction in SASH1 expression, compared to normal colon mucosa.

Decreased SASH1 mRNA expression was correlated with the occurrence of metachronous distant metastasis, and multivariate analysis identified SASH1 downregulation as an independent negative prognostic parameter for patient survival (Rimkus et al., 2006). Recently, these results were confirmed on an independent patient collective of stage II colon cancer (n=179 patients), confirming that decreased SASH1 expression is an independent negative prognostic factor in colon cancer, allowing to distinguish high-risk patients in early, locally restricted stages of the disease (Nitsche et al., 2012).

### **Pancreatic cancer (unpublished observations)**

#### **Note**

In a collective of n=103 patients with pancreatic ductal adenocarcinoma, 38% of the tumors showed no or strongly reduced SASH1 protein expression by immunohistochemistry. Decreased SASH1 expression was significantly reduced with poor survival in Kaplan-Meier analysis (Tiago de Oliveira and Klaus-Peter Janssen, unpublished data).

### **Benign dyskeratosis**

#### **Note**

SASH1 germline mutations have been identified in patients with a kind of dyschromatosis. Of note, three independent heterozygous germline mutations have been identified, that cause amino acid substitutions in the central SH3/SAM-containing region in the SASH1 gene. In epidermal tissues

from an affected individual, increased transepithelial migration of melanocytes was observed (Zhou et al., 2013).

### **Osteosarcoma**

#### **Note**

SASH1 protein was significantly down-regulated in osteosarcoma tissues compared to normal bone tissue. Moreover, SASH1 protein showed significant down-regulation in osteosarcoma tissues from patients with lung metastasis compared to those without lung metastasis, and, lastly, a gradual decrease of SASH1 expression occurred with increasing Enneking stage (Meng et al., 2013).

## **References**

- Zeller C, Hinzmann B, Seitz S, Prokoph H, Burkhard-Goettges E, Fischer J, Jandrig B, Schwarz LE, Rosenthal A, Scherneck S. SASH1: a candidate tumor suppressor gene on chromosome 6q24.3 is downregulated in breast cancer. *Oncogene*. 2003 May 15;22(19):2972-83
- Rimkus C, Martini M, Friederichs J, Rosenberg R, Doll D, Siewert JR, Holzmann B, Janssen KP. Prognostic significance of downregulated expression of the candidate tumour suppressor gene SASH1 in colon cancer. *Br J Cancer*. 2006 Nov 20;95(10):1419-23
- Martini M, Gnann A, Scheikl D, Holzmann B, Janssen KP. The candidate tumor suppressor SASH1 interacts with the actin cytoskeleton and stimulates cell-matrix adhesion. *Int J Biochem Cell Biol*. 2011 Nov;43(11):1630-40
- Chen EG, Chen Y, Dong LL, Zhang JS. Effects of SASH1 on lung cancer cell proliferation, apoptosis, and invasion in vitro. *Tumour Biol*. 2012 Oct;33(5):1393-401
- Lin S, Zhang J, Xu J, Wang H, Sang Q, Xing Q, He L. Effects of SASH1 on melanoma cell proliferation and apoptosis in vitro. *Mol Med Rep*. 2012 Dec;6(6):1243-8
- Nitsche U, Rosenberg R, Balmert A, Schuster T, Slotta-Huspenina J, Herrmann P, Bader FG, Friess H, Schlag PM, Stein U, Janssen KP. Integrative marker analysis allows risk assessment for metastasis in stage II colon cancer. *Ann Surg*. 2012 Nov;256(5):763-71; discussion 771
- Yang L, Liu M, Gu Z, Chen J, Yan Y, Li J. Overexpression of SASH1 related to the decreased invasion ability of human glioma U251 cells. *Tumour Biol*. 2012 Dec;33(6):2255-63
- Meng Q, Zheng M, Liu H, Song C, Zhang W, Yan J, Qin L, Liu X. SASH1 regulates proliferation, apoptosis, and invasion of osteosarcoma cell. *Mol Cell Biochem*. 2013 Jan;373(1-2):201-10
- Zhou D, Wei Z, Deng S, Wang T, Zai M, Wang H, Guo L, Zhang J, Zhong H, He L, Xing Q. SASH1 regulates melanocyte transepithelial migration through a novel Gas-SASH1-IQGAP1-E-Cadherin dependent pathway. *Cell Signal*. 2013 Jun;25(6):1526-38

---

*This article should be referenced as such:*

Janssen KP. SASH1 (SAM and SH3 domain containing 1). *Atlas Genet Cytogenet Oncol Haematol*. 2014; 18(4):236-238.

---