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Gene Section
Review

ASH2L (ash2 (absent, small, or homeotic)-like (Drosophila))

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Identity

Other names: ASH2, ASH2L1, ASH2L2, Bre2

HGNC (Hugo): ASH2L

Location: 8p11.23

DNA/RNA

Description

16 exons spanning over 34218 base pairs.

Transcription

mRNA is 2368 base pairs long.

Protein

Description

There are three known isoforms of ASH2L (Wang et al., 2001). Isoform 1 is considered the canonical sequence and consists of 628 amino acids (Wang et al., 2001). Isoform 2 is missing amino acids 1-94 and 541-573 from isoform 1 (Wang et al., 2001). Isoform 3 is missing the amino acids 1-94 from isoform 1 (figure 2) (Wang et al., 2001). There are four identified domains within ASH2L which include a N-terminus containing a PHD finger and a winged helix motif (WH) and the C-terminus containing a SPRY domain and the **S**dc1 **D**PY-30 **I**nteracting domain (SDI) (figure 2) (Chen et al., 2011; Roguev et al., 2001; Sarvan et al., 2011; South et al., 2010; Wang et al., 2001). The largest of the three identified domains within ASH2L is the SPRY domain, which is also conserved from yeast to humans. SPRY domains were originally named after the **SP**Ia kinase and the **RY**anodine receptor proteins in which it was first identified (Rhodes et al., 2005). Crystal structures of SPRY domain containing proteins show primarily a beta-sandwich structure with extending loops (Filippakopoulos et al., 2010; Kuang et al., 2009; Simonet et al., 2007; Woo et al., 2006b). The SPRY domain is thought to be a specific protein-protein interaction domain

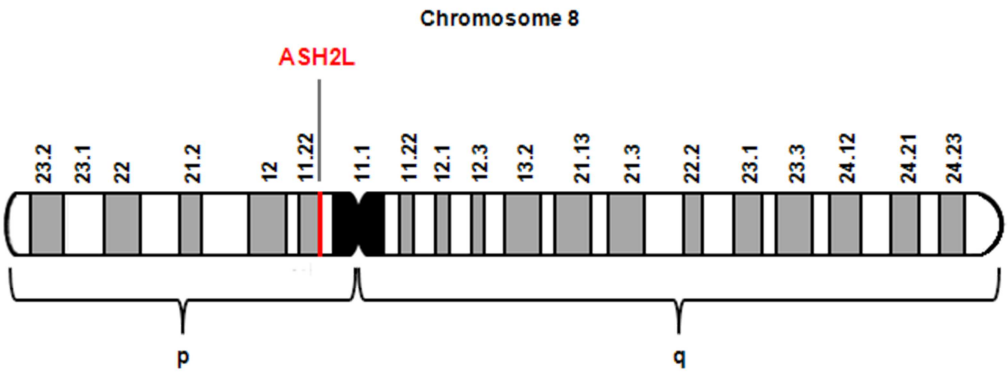

Figure 1. Map of chromosome 8 with region 8p11.2 highlighted as the location of the gene ASH2L.

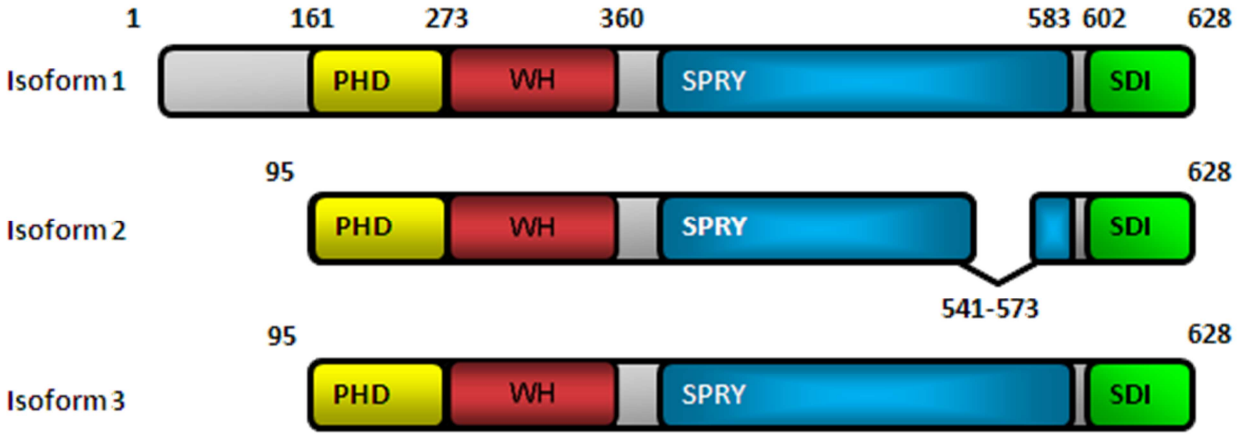

Figure 2. Schematic model of the three known isoforms of ASH2L and the amino acid sequence changes compared to the canonical isoform 1 (aa 1-628). The positions of known domains within ASH2L are displayed. PHD finger (aa 95-161), WH motif (aa 162-273), SPRY domain (aa 360-583), and SDI domain (aa 602-628). Isoform 2 and 3 are numbered according to isoform 1.

with specific partners, but instead of recognizing a particular motif or interaction domain the SPRY domain binds to interaction partners using non-conserved binding loops (Filippakopoulos et al., 2010; Woo et al., 2006a; Woo et al., 2006b). Recent work has shown that the C-terminus of ASH2L that contains the SPRY domain and the SDI domain are able to interact with the other MLL complex member RBBP5 in vitro (Avdic et al., 2011).

ASH2L also contains a putative Plant Homeo Domain (PHD) finger in its N-terminus (Wang et al., 2001). The structure of PHD fingers shows that conserved cysteine and histidine residues bind to Zn^{2+} ions (Champagne et al., 2008; Champagne and Kutateladze, 2009; van Ingen et al., 2008). There is no known function attributed to the PHD finger in ASH2L, though in conjunction with the winged helix motif it may be necessary for DNA binding.

The N-terminal winged helix (WH) motif was recently discovered when the crystal structure of the N-terminus of ASH2L was solved (Chen et al., 2011; Sarvan et al., 2011). Using in vitro DNA binding analyses as well as chromatin immunoprecipitation, it was determined that ASH2L can bind DNA at the HS2 promoter region and the beta-globin locus as well as non-specific DNA sequence (Chen et al., 2011; Sarvan et al., 2011).

The last identifiable domain within ASH2L is the SDI domain. There is no structural information on the SDI domain but the functional importance was determined biochemically. The function of the SDI domain was determined using in vitro binding experiments. ASH2L was shown to directly interact with DPY-30 without any additional MLL or Set1 complex components (South et al., 2010). The function of the SDI domain is conserved from yeast to humans because the yeast ASH2L homolog Bre2 was also shown to interact with the DPY-30 homolog Sdc1 (South et al., 2010). There are conserved hydrophobic residues in both the SDI domain of ASH2L and the Dpy-30 domain of DPY-30 that are important for binding, which suggests that the interaction between the SDI domain of ASH2L and the DPY-30 domain of DPY-30 is through hydrophobic interactions (South et al., 2010).

Expression

Northern blot analysis from multiple tissues revealed that ASH2L expression is expressed in 14 different tissue types with the highest expression in fetal liver and testes (Lüscher-Firzlaff et al., 2008). ASH2L transcripts were also found to be expressed higher in various Leukemia cell lines, such as K562, Hel, and Dami cells (Lüscher-Firzlaff et al., 2008).

Localisation

Nucleus.

Function

Biochemical data has shown that ASH2L is found in a methyltransferase core complex composed of ASH2L, RBBP5, DPY30, WDR5, and the catalytic SET domain containing protein. This core complex is highly conserved and similar to the budding yeast Set1 complex that consists of Set1 (MLL/SET1), Bre2 (ASH2L), Swd1 (RBBP5), Swd3 (WDR5), Swd2 (WDR82), Sdc1 (DPY-30), Spp1 (CFP1/CGBP). ASH2L is also known to associate with numerous additional factors. Many of these additional factors are thought to associate with ASH2L and the H3K4 methyltransferase complexes to target the complex to specific sites within the genome (Cho et al., 2007; Dou et al., 2006; Hughes et al., 2004; Steward et al., 2006; Stoller et al., 2010). Knock-down of ASH2L using siRNA globally decreases H3K4 trimethylation (Dou et al., 2006; Steward et al., 2006). ASH2L and H3K4 methylation both appear to play a key role in oncogenesis (Hess, 2006). ASH2L is found to be over abundant in many cancer cell lines and knock-down of ASH2L by siRNA can prevent tumorigenesis (Lüscher-Firzlaff et al., 2008). Recent work has suggested that ASH2L in combination with WDR5 and RBBP5 exhibits H3K4 methyltransferase activity (Cao et al.,

2010; Patel et al., 2009; Patel et al., 2011). In addition, this catalytic activity is not dependent on the SET domain containing proteins such as MLL1 (Cao et al., 2010; Patel et al., 2009; Patel et al., 2011).
Alternative to ASH2L's function in H3K4 methylation ASH2L may also be playing a role in endosomal trafficking (Xu et al., 2009). ASH2L, DPY-30 and WDR5 were originally implicated in endosomal trafficking when siRNA knock-down of these genes increased the amount of internalized CD8-CIMPR and overexpression increased the amount of cells displaying a altered CIMPR distribution (Xu et al., 2009).

Homology

ASH2L has homologs in eukaryotes from yeast to humans.

Implicated in

Various cancers

Note

ASH2L mRNA expression does not appear to be misregulated in human cancer cell or primary cell lines. However, expression of ASH2L protein is increased in many cancer cell lines as well as tumor samples (Lüscher-Firzlaff et al., 2008). There was detectable increased staining in the nucleus of ASH2L protein in a wide array of tumors including squamous cell carcinoma of the larynx and the cervix, melanomas, adenocarcinoma of the pancreas, and acinar and ductal breast cancers (Lüscher-Firzlaff et al., 2008). ASH2L protein appears to be more stable in cancer cell lines compared to the normal cell line counterparts and knockdown of ASH2L can prevent tumerogenesis suggesting a role in tumor cell proliferation (Lüscher-Firzlaff et al., 2008).

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