Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Review

ASXL1 (additional sex combs like 1 (Drosophila))

Marie-Joelle Mozziconacci, Daniel Birnbaum

Institut Paoli-Calmettes, Centre de Recherche en Cancerologie de Marseille, Departement de Biopathologie and Laboratoire d'Oncologie Moleculaire, 232 Boulevard de Sainte-Marguerite, 13009 Marseille, France (MJM), Laboratoire d'Oncologie Moleculaire, Centre de Recherche en Cancerologie de Marseille, UMR891 Inserm, Institut Paoli-Calmettes 232 Boulevard de Sainte-Marguerite 13009 Marseille, France (DB)

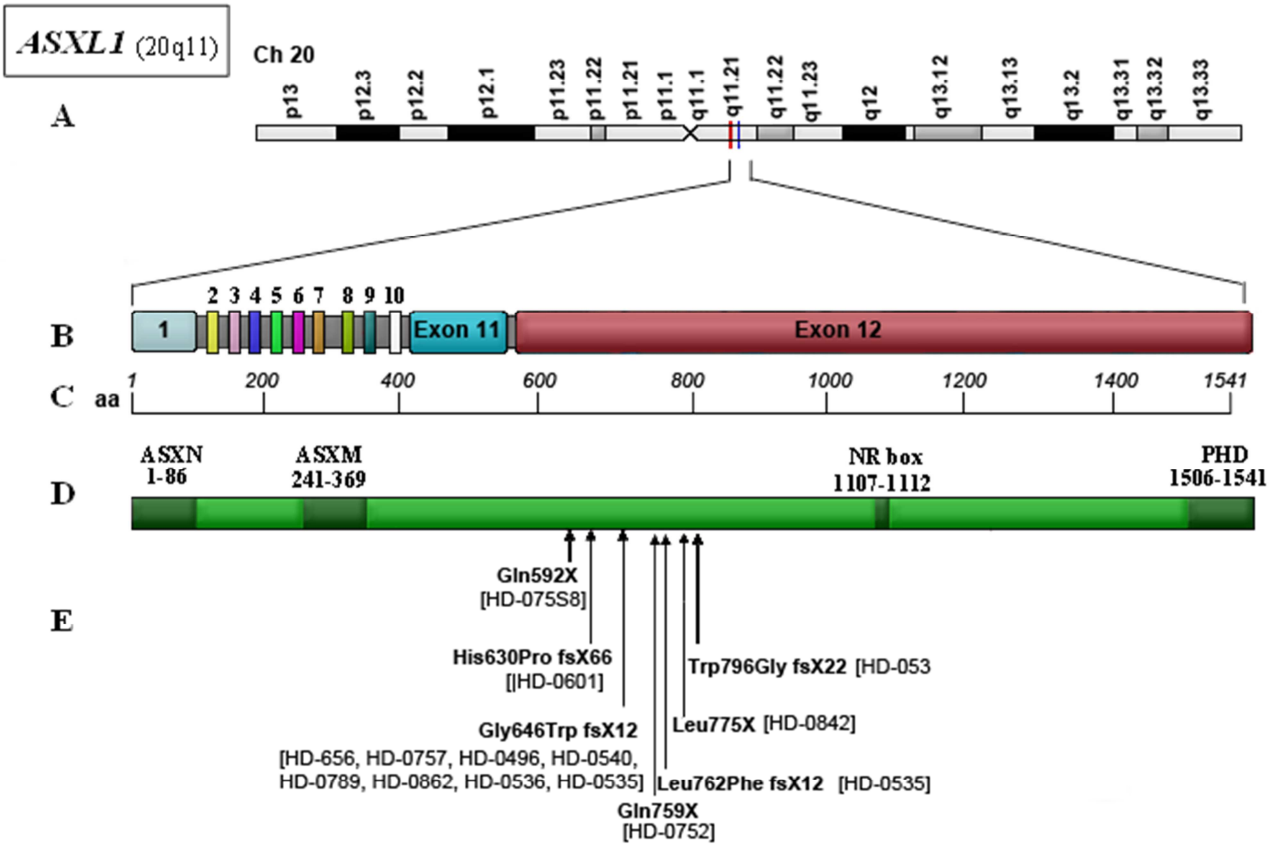
Published in Atlas Database: August 2010

Online updated version : http://AtlasGeneticsOncology.org/Genes/ASXL1ID44553ch20q11.html
DOI: 10.4267/2042/45011

Identity

Other names: KIAA0978, MGC117280, MGC71111
HGNC (Hugo): ASXL1

Location: 20q11.21
Local order: centromere 5' - 3' telomere.



Representation of ASXL1 locus. A: Chromosome 20 with localisation of ASXL1; **B:** ASXL1 gene; **C:** Amino acid count; **D:** Protein with domains. ASXN, conserved domain at the N-terminus; ASXM, conserved domain in the middle part; NR, nuclear receptor; PHD, plant homeodomain; E: examples of mutations.

DNA/RNA

Description

The ASXL1 gene spans around 80 kb of genomic DNA and is composed of 12 exons.

Transcription

Alternative splicing results in multiple transcript variants.

Protein

Description

The longer ASXL1 transcript encodes a 1541 amino acid (170 kDa) protein. Mammalian ASXL proteins are characterized by an amino-terminal ASX homology (ASXH) region containing 2 putative nuclear receptor coregulator binding motifs (NR box), 3 other NR box motifs and a C-terminal plant homeodomain protein-protein interaction domain. Contains one Leu-Xaa-Xaa-Leu-Leu (LXXLL) motif, which may be required for an association with nuclear receptors.

Expression

ASXL1 is expressed all hematopoietic cell fractions in mice. Asxl1 knockout mice exhibit mild defects in differentiation of lymphoid and myeloid progenitors, but not in multipotent progenitors and do not develop MDS or other hematological malignancy.
ASXL1 is widely expressed at low level in heart, brain, skeletal muscle, placenta, pancreas, spleen, prostate, small intestine, colon, peripheral blood, leukocytes, bone marrow and fetal liver. Highly expressed in testes.

Localisation

Nucleus (probable).

Function

- ASXL1 acts as a co-regulator of retinoic acid (RA) receptor in RA sensitive cell lines, and as a co-repressor of RA receptor in RA resistant cell lines. Either a coactivator or corepressor for the retinoid receptors retinoic acid receptor and retinoid X receptor in a cell type-specific manner.
- ASXL1 cooperates with HP1 (heterochromatin protein 1) to modulate histone H3 demethylase LSD1 activity, leading to a change in histone H3 methylation and RAR repression.
- ASXL1 belongs to the Enhancer of Trithorax and Polycomb (ETP) group in drosophila.
- ASXL1 is required for maintenance of both activation and silencing of Hox genes in mice and drosophila in a context-dependent manner.
- ASXL1 is one of the fusion protein partners of PAX5 in B-cell precursor acute lymphoblastic leukemias.
- ASXL1 may function as a tumor suppressor in myeloid malignancies by affecting stem or progenitor cell self renewal or differentiation.

Homology

There are 3 mammalian homologs of the Additional sex combs (Asx) gene of Drosophila: ASXL1, 2 (chromosome 2p24 in humans) and 3 (chromosome 18q11 in humans).

Mutations

Note

Acquired ASXL1 mutations are frequently frameshift and nonsense. All mutations are in exon 12, mostly around the Gly-rich domain (amino acids 642-685). The most common somatic mutation is p.Gly646Trpfsx12.
These mutations cause truncation of the ASXL1 protein downstream of the ASXH domain leading to the loss of the C-terminal PHD domain.
Some possible single nucleotide polymorphisms have been described:
p.Arg1224Thr, p.Thr769Ala, p.Gly1007Arg, p.Thr688Met, p.Gln1074Leu, p.Arg693Gly, p.T1139K, p.Gly652Ser, p.Val1072Asp...
All mutations have been found in myeloid diseases so far. A fusion has been found in B-cell leukemia.

Implicated in

Myelodysplastic syndromes (11-21%)

Note

Mutations p.Arg596Profsx23, p.Gly646Trpfsx12 (the most common mutation), p.Gln1102Asp, p.Leu1395Val, p.Ser1457Profsx18...

Prognosis

More frequent in advanced and high-risk MDSs (>40% in RAEB2).

Cytogenetics

Normal or abnormal karyotype.

Chronic myelomonocytic leukemia (33-43%)

Note

p.His630Profsx66, p.Lys618X, p.Gly646trpfsx12, p.Gln768X, p.Thr836Leufsx2, p.Ser846Glnfsx5, p.Lys888Glufsx6, p.Arg1068X, p.pro1263Glnfsx17, p.Leu1266Hisfsx9, p.Thr1271lysfsx10...

Prognosis

Associated with acute transformation.

Cytogenetics

Normal or abnormal karyotype. More common in patients with -7/7q-. Infrequent in the presence of -5/5q-.

Juvenile myelomonocytic leukemia (JMML) (2/49 patients 4%)

Note

p.Arg693X, p.Ser846ValfsX21.

Cytogenetics
Normal karyotype or monosomy 7.

Acute myeloid leukemia (20-30%)

Note
30% in primary AMLs, 47% in secondary AMLs and 23% in post-MDS AMLs.

Prognosis
Shorter overall survival.

Cytogenetics
Normal or abnormal karyotype, associated with trisomy 8, inversely correlated with NPM1 mutation.

Myeloproliferative neoplasms (8%)

Note
Present in all forms, including chronic myeloid leukemia. More frequent in primary myelofibrosis.

Prognosis
Occur in both chronic and blast-phase MPNs.

B-cell acute lymphoblastic leukemia

Cytogenetics
Dicentric chromosome dic(9;20)(p11-13;q11).

Hybrid/Mutated gene
PAX5 on 9p and ASXL1 on 20q.

To be noted

Note
ASXL1 can be altered by small local deletion detected only by array CGH or SNP arrays. However, ASXL1 seems to be centromeric to the main deleted region in classical 20q deletion.

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This article should be referenced as such:

Mozziconacci MJ, Birnbaum D. ASXL1 (additional sex combs like 1 (Drosophila)). Atlas Genet Cytogenet Oncol Haematol. 2011; 15(5):391-394.