

Gene Section

Review

ARID1A (AT rich interactive domain 1A (SWI-like))

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Abstract

Review on ARID1A, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: B120, BAF250, BAF250a, BM029, C1orf4, ELD, MRD14, OSA1, P270, SMARCF1, hELD, hOSA1

HGNC (Hugo): ARID1A

Location: 1p36.11

Local order: Gene orientation: telomere-3' ARID1A 5'-centromere.

DNA/RNA

Description

ARID1A gene is encoded by 20 exons spanning 86,08 Mb.

Transcription

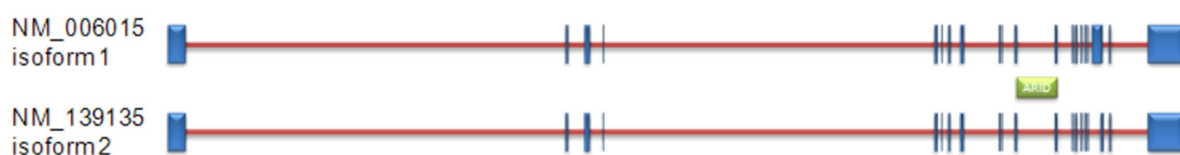
Human ARID1A has 2 transcript variants. The long variant (isoform 1) transcribed into 8585 bp mRNA, the coding sequence is from 374 bp - 7231 bp.

The short variant (isoform 2) transcribed into 7934 bp mRNA, the coding sequence is from 374 bp - 6580 bp. Isoform 2 has a shorter exon 18 compared to isoform 1.

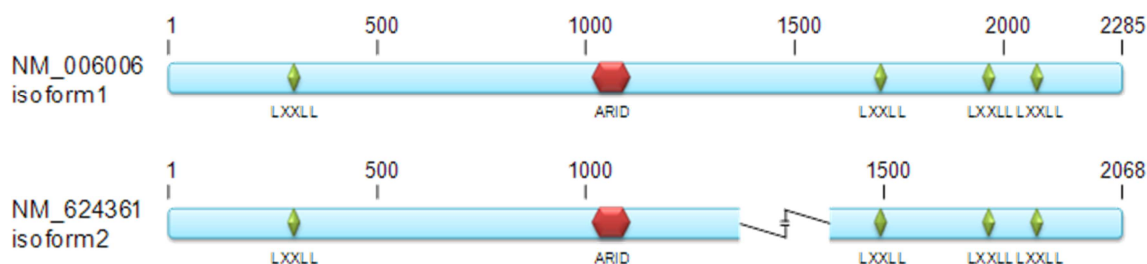
Protein

Note

The longer isoform of ARID1A consists of 2285 amino acids (pI: 6.24), with predicted molecular mass of 242,04 kDa. The shorter isoform of ARID1A consists of 2068 amino acids (pI: 6.08), with predicted molecular mass of 218,33 kDa. Both isoforms contain a single "ARID" DNA binding domain and four "LXXLL" nuclear receptor coactivator motifs.



DNA organization of ARID1A.



ARID1A protein.

Description

ARID1A is a member of the SWI/SNF family that can regulate genes transcription by chromatin structure alteration through its helicase and ATPase activities. The encoded ARID1A nuclear protein is part of the BRG/BRM chromatin remodeling complex that has been shown to play an integral role in controlling gene expression.

Expression

Ubiquitously expressed in various normal tissues, with the highest expression seen in brain, blood and female tissues.

Localisation

Mainly located at cell nucleus but not at nucleolus.

Function

ARID1A contains a conserved DNA-binding domain (ARID) that could be important for its function and can specifically bind an AT-rich DNA sequence. ARID1A is part of the large ATP-dependent chromatin remodeling complex SNF/SWI, which is required for transcriptional activation of genes. Changes in this SNF/SWI complex has been implicated in many cellular processes, including development, differentiation, proliferation, DNA repair, and tumor suppression. ARID1A has been reported to act as tumor suppressor in gynecological cancers (Guan et al., 2011b). Molecular studies using over-expression and RNAi silencing models have demonstrated that ARID1A negatively regulates cellular proliferation and tumorigenicity. This negative regulation is achieved through molecular collaboration between ARID1A/BRG1 and p53, to regulate tumor-inhibiting p53-downstream target genes such as CDKN1A and SMAD3. Using mutational studies, Guan et al. (2012) have further confirmed ARID1A role as tumor suppressor, with all of the in-frame indel mutants have lost their ability to inhibit cellular proliferation.

Mutations

Germinal

ARID1A mutations have been implicated in Coffin-Siris syndrome, a rare genetic disorder that causes

developmental delay and abnormalities in 5th fingers or toes (Tsurusaki et al., 2012; Santen et al., 2013; Wieczorek et al., 2013).

Somatic

ARID1A is located at chromosome 1p that is frequently deleted in tumours. ARID1A sequence mutations, deletions, and rearrangements were identified in ovarian, kidney, breast, lung, pancreatic and stomach cancer.

Implicated in

Ovarian clear cell carcinoma

Oncogenesis

ARID1A somatic mutations were identified in 57% of the 42 ovarian clear cell carcinomas (Jones et al., 2010). Maeda et al. (2010) has demonstrated that ARID1a genetic mutations resulted in loss of ARID1A protein expression in 59% of the 149 ovarian clear cell carcinomas.

Study with a larger cohort of 210 patient samples has also demonstrated that ARID1A somatic mutation were found in 46% of patients with ovarian clear-cell carcinoma and 30% of patients ovarian endometrioid carcinoma (Wiegand et al., 2010).

ARID1A inactivation by ARID1A mutations has been suggested as an early molecular event that can lead to tumor progression from benign ovarian endometrioid cysts into an aggressive ovarian clear cell and endometrioid carcinoma (Ayhan et al., 2012).

Uterine endometrioid carcinoma

Oncogenesis

ARID1A mutations were observed in 40% of uterine endometrioid carcinoma with none presented in uterine serous carcinomas (Guan et al., 2011a). All of the mutations in endometrioid carcinomas were the nonsense or insertion/deletion types (Guan et al., 2011a) and expected to result in complete loss or clonal loss of ARID1A expression. Immunostaining confirmed the relatively significant frequency of loss of ARID1A protein expression with 25-26% and 44% in uterine low-grade and high-grade endometrioid carcinomas, respectively (Guan et al., 2011a; Werner et al., 2013; Mao et al.,

2013). Hence, mutation-related loss of ARID1A expression has also been hypothesized as an early event and played an important role in tumor progression of uterine endometrioid carcinoma (Ayhan et al., 2012; Werner et al., 2013; Mao et al., 2013).

Cervical cancer

Oncogenesis

Loss of ARID1A protein expression was observed in 31% (14/45) of cervical adenocarcinomas/adenosquamous carcinomas with no correlation to any clinicopathological features (Katagiri et al., 2012). Later studies using a large series of cervical cancer tissue specimens, ARID1A expression was found to be significantly decreased in cervical cancer tissues than in non-adjacent normal cervical epithelial tissues (Cho et al., 2013). The decrease of ARID1A expression was also found to be associated with transition from normal cells to cervical carcinoma and a more aggressive tumor phenotype (Cho et al., 2013). Overall survival was also found to be reduced in cervical cancer patients with loss of ARID1A (Cho et al., 2013).

Breast cancer

Oncogenesis

Low ARID1A expression was observed in 56% (63/112) of the breast cancers samples and was significantly associated with advanced tumor stage, higher P53 expression, increase Ki-67 and triple negative (ER/PR/Her-2⁻) molecular subtype (Zhang et al., 2012; Mamo et al., 2012). Low ARID1A expression was a predictor of poor overall survival of breast cancer patients (Zhang et al., 2012; Mamo et al., 2012). Breast cancer also exhibited a low rate (3-4%) of ARID1A mutations (Jones et al., 2010; Cornen et al., 2012).

Gastric cancer

Oncogenesis

Inactivating mutation of ARID1A has also been identified gastric cancer (Wang et al., 2011; Abe et al., 2012; Zhang et al., 2012). Loss of ARID1A expression has been correlated with increasing depth of tumor infiltration, higher tumor grade, and poor overall patient survival (Abe et al., 2012; Wang et al., 2012). Moreover, ARID1A expression has been shown as an independent prognostic factor of overall survival in multiple studies (Abe et al., 2012; Wang et al., 2012).

Coffin-Siris syndrome

Prognosis

Hepatoblastoma and multiple congenital anomalies.

Oncogenesis

ARID1A mutations in individual with Coffin-Siris syndrome lead to a truncation and nonfunctional

ARID1A protein (Tsurusaki et al., 2012; Santen et al., 2013; Wiczorek et al., 2013). As a result, affected individuals developed abnormalities, such as missing the fifth fingers or toes and coarse characteristic of facial features. Moreover, cancer was not detected in any of the individual with ARID1A mutation, reported in this study.

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