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Gene Section
Mini Review

UBE3A (ubiquitin protein ligase E3A)

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Identity

Other names: ANCR, AS, E6-AP, EPVE6AP, FLJ26981, HPVE6A
HGNC (Hugo): UBE3A
Location: 15q11.2

DNA/RNA

Description

The UBE3A gene is located on Chr. 15 (23133489-23235221); 13 exons.

Transcription

3 Isoforms through alternative splicing; mRNA Isoform 1: 4491 bp, ORF: 2556 bp; mRNA Isoform 2: 4516 bp, ORF: 2625 bp; mRNA Isoform 3: 5164 bp, ORF: 2616 bp.

Protein

Description

The UBE3A gene product is commonly referred to as E6AP (E6 associated protein).
Isoform 1: 852 amino acids, Isoform 2: 875 amino acids, Isoform 3: 872 amino acids. Migration in SDS-PAGE with an approximate molecular mass of 100 kDa.
HECT (Homologous to the E6AP C terminus) domain: amino acids 500-852; Active cysteine residue at position 820 (amino acid positions refer to Isoform 1).
Posttranslational modifications: ubiquitylation.
Binding partners and interaction sites on E6AP: Human papillomavirus (HPV) E6 oncoprotein: amino acids 378-395; Herc2 (unpublished): amino

acids 150-200; Steroid hormone receptors (AR, ER, PR): amino acids 386-390 and 638-642 (LxxLL motif); Hepatitis C virus core protein: amino acids 395-494 (amino acid positions refer to Isoform 1).

Expression

Monoallelically expressed (maternal allele) in Purkinje neurons, a subset of hippocampal neurons, and neurons of the olfactory bulb. Biallelically expressed in most other tissues.

Localisation

Predominantly cytoplasmic.

Function

Ubiquitin-protein ligase. In complex with the E6 oncoprotein of cervical cancer-associated HPVs, E6AP targets p53 and other cellular proteins (e.g. hDLG, Scribble, E6TP1, NFX1-91) for ubiquitylation and proteasomal degradation. E6-independent substrates include HHR23A and HHR23B, BLK, BAK, MCM7, and AIB1. Loss-of-function results in Angelman Syndrome.
Coactivator of the nuclear hormone receptor superfamily. This function appears to be independent of the ubiquitin ligase function and its role in human disease remains unknown.

Homology

E6AP shares homology from fly to man and is highly conserved in vertebrates.

Mutations

Note
All known disease-associated mutations (maternal allele) result in an inactivation of the ubiquitin ligase function and have been etiologically associated with the Angelman Syndrome. Mutations in the UBE3A gene have not been associated with cancer development.

Implicated in

Cervical Cancer

Oncogenesis

The E6 oncoprotein of so-called high risk HPVs that have been etiologically associated with malignant lesion of the anogenital tract (most notably, cervical cancer) have the ability to bind to E6AP. The E6/E6AP complex binds to the p53 tumor suppressor, thereby targeting p53 for ubiquitylation and proteasomal degradation. It is commonly assumed that this (p53 degradation and, thus, inactivation) represents a critical step in the development of cervical cancer. Although additional targets of the E6/E6AP complex have been described (see above), the relevance of these interactions for cervical carcinogenesis is currently unclear. Furthermore, E6AP itself is a target for E6-dependent autoubiquitylation and degradation. However, if this contributes to HPV-induced cervical carcinogenesis is currently unknown.

Angelman Syndrome

Disease

Angelman Syndrome is a severe neurological disorder, genetically linked to UBE3A. Almost 95% of all known mutations hit the maternal UBE3A allele or its relevant imprinting center, resulting in inactivation of the ubiquitin ligase function of E6AP.

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