ASPM (asp (abnormal spindle) homolog, microcephaly associated (Drosophila))

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Identity

Other names: ASP; Calmbp1; DKFZp686N06184; FLJ10517; FLJ10549; FLJ43117; MCPH5
HGNC (Hugo): ASPM
Location: 1q31.3
Local order: Several genes flanking ASPM arranged by an order of centromere to telomere are:
KCNT2 (1q31.3) (potassium channel, subfamily T, member 2); CFH (1q32) (complement factor H);
CFHR3 (1q32) (complement factor H-related 3);
CFHR1 (1q32) (complement factor H-related 1);
CFHR4 (1q32) (complement factor H-related 4);
CFHR2 (1q31-q32.1) (complement factor H-related 2);
CFHR5 (1q22-q23) (complement factor H-related 5);
F13B (1q31-q32.1) (coagulation factor XIII, B polypeptide); ASPM (1q31) (asp (abnormal spindle) homolog, microcephaly associated (Drosophila)); ZBTB41 (1q31.3) (zinc finger and BTB domain containing 41); LOC127011 (1q31.3) (similar to ATPase, H+ transporting, lysosomal accessory protein 2); MRPS21P3 (1q31.2) (mitochondrial ribosomal protein S21 pseudogene 3); CRB1 (1q31-q32.1) (crumbs homolog 1 (Drosophila)); C1orf218 (1q31.3) (chromosome 1 open reading frame 218); DENND1B (1q31.3) (DENN/MADD domain containing 1B); LOC730232 (1q31.3) (similar to eukaryotic translation elongation factor 1 alpha 1); LOC100129017 (1q31.3) (hypothetical LOC100129017); C1orf53 (1q31.3) (chromosome 1 open reading frame 53); LHX9 (1q31-q32) (LIM homeobox 9); LOC647195 (1q31.3) (hypothetical LOC647195); NEK7 (1q31.3) (NIMA (never in mitosis gene a)-related kinase 7).

Genomic organization of the ASPM gene on chromosome 1q.

Genomic diagram of ASPM gene. Exons are represented by boxes on the diagram.
**DNA/RNA**

**Description**
ASPM, maps to NC_000001.10 in human genome, contains 28 exons with a 10,434 base pairs ORF (NCBI GenBank accession number AF509326), spanning a region of 62,568 base pairs at chromosome 1q31.

**Transcription**
ASPM encodes a 10906 bps mRNA, (NM_018136.4), in a telomeric to centromeric orientation and the coding region is from 258 bp to 10961bp (10434 bp). 5' part of exon 1 and 3' part of exon 28 are non-coding. The 28 exons of ASPM mRNA are 554, 144, 1480, 105, 147, 246, 68, 142, 131, 176, 146, 86, 222, 208, 143, 129, 195, 4755, 167, 97, 210, 150, 192, 193, 155, 177, 170, 300 base pairs, respectively.

**Pseudogene**
None.

**Protein**

**Description**
The 10434 bps ORF of ASPM mRNA translates a 3477 amino acid protein with a calculated molecular weight of 409.8 kDa. The main ASPM isoform protein, from N-terminal, begins with a microtubule binding domain, followed by two calponin homology (CH) domains, which are possibly responsible for transportation of the ASPM protein to the spindle poles. The third part is IQ (I for isoleucine, Q for glutamine) repeats region which is the calmodulin binding domains. The numbers of IQ repeats are identified up to 81, at position 1273 to 3243. The C-terminal of ASPM is an armadillo-like domain of unknown function.

**Expression**
ASPM transcripts were detected in a variety of human embryo tissues (brain, bladder, colon, heart, liver, lung, skeletal muscle, skin, spleen and stomach), and in adult tissues except for the adult brain, but with much lower amount.

ASPM isoforms were generated by alternative splicing. The brain-specific isoform, main ASPM isoform corresponds to a 3477 amino acid residue protein (410 kDa) containing 81 IQ motifs. Alternatively spliced human ASPM variants code for different numbers of IQ domains. Two major ASPM transcripts with sizes of 10.3 and 5.7 kb were identified in all tissues analyzed. The spliced variants of ASPM with variable sizes were also detected in fetus tissue.

**Localisation**
ASPM protein, a component of the mitotic spindle, localizes to the centrosome in interphase and to the spindle poles from prophase through telophase.

**Function**
ASPM is a spindle pole/centrosome protein, essential for neurogenic mitosis and possibly controlling the fate-switch to asymmetric cell division through the position of the centrosome at mitosis. The brain-specific main ASPM isoform protein appears to be pivotal for the expansion of cerebral cortical size. Other spliced variants contain different IQ domains or lacking both CH domains and a part of the IQ motifs may be potentially with different functions. One of the smaller proteins detected in cell extracts may be the ASPM product required for mitosis by all dividing cells.

**Homology**
According to protein identities compared with Human ASPM:
- Pan troglodytes: ASPM; (3443/3477, 99%)
- Canis lupus familiaris: ASPM; (2738/3392, 80%)
- Bos taurus: ASPM; (2557/3484, 73%)
- Mus musculus: Aspm; (1882/2948, 63%)
- Rattus norvegicus: Aspm; (1851/2939, 62%)
- Danio rerio: aspm; (1390/3554, 39%)

ASPM protein contains 2 calponin homology (CH) domains and 81 IQ repeats domain. Total 81 distinct IQ motifs were found at position 1273 to 3243. Numbers indicate the amino acid numbers.
Mutations of ASPM in MCPH. According to Nicholas et al. 2009, all reported autosomal recessive primary microcephaly (MCPH) mutations in ASPM have been presented in this table by different kind of mutations, including nonsense mutations, deletions, insertions and mutations in the splicing region. The reference sequence of mutation sites is according to NM_018336.3.
Implicated in

**Primary autosomal recessive microcephaly (MCPH)**

**Note**

Primary autosomal recessive microcephaly is a neurodevelopment disorder due to the consequence of deficient neurogenesis within the neurogenic epithelium, resulting in congenital microcephaly (reduced brain size) and mental retardation. MCPH is the consequence of impairment in mitotic spindle regulation in cortical progenitors due to mutations in ASPM.

Homzygous mutations in the ASPM gene, located at MCPH5 locus on chromosome 1q31, are the most common cause of MCPH particularly in the Pakistani population. ASPM mutations are restricted to individuals with an MCPH, no defects other than microcephaly are found in patients carrying mutations in this gene. So far, the phenotypic differences in people with different versions of these genes were not found.

**Hepatocellular carcinoma**

**Note**

ASPM, a component of the mitotic spindle, is shown to express in many human malignant cells nearly and all transformed human cell lines, suggesting that ASPM play an important role in cell proliferation in tumorigenesis.

ASPM mRNA was overexpressed in human hepatocellular carcinoma (HCC), but was very low or undetectable in adult liver, and in benign hepatic tumors, such as hepatocellular adenoma and focal nodular hyperplasia. The overexpression of ASPM correlated with higher-grade (grade II-IV), high-stage (stage IIIA-IV) which had vascular invasion and poor prognosis of HCC. In addition, ASPM overexpression is the most important molecular factor associated with ETR (early tumor recurrence) (intrahepatic tumor recurrence and/or distant metastasis within 12 months after HCC tumor resection), and could be used as a molecular marker predicting enhanced invasive/metastatic potential of HCC.

**Glioblastoma**

**Note**

ASPM is essential for normal mitotic spindle function in embryonic neuroblasts, and is recognized as a critical regulator of brain size, it may play a role in promoting neuroblast proliferation. Using gene coexpression module in glioblastoma, ASPM was identified as a key gene of glioblastoma, its overexpression was demonstrated in glioblastoma relative to normal brain. siRNA-mediated ASPM knockdown inhibits neural stem cell self-renewal and turn forward neural stem cell differentiation. ASPM knockdown also inhibits cell growth of U87-EGFR\*III cells (glioblastoma cells) and the low passage explant culture from a glioblastoma patient. Those results suggesting that ASPM is a potential molecular target in glioblastoma that resulting in the overexpression of ASPM in glioblastoma.

**Cancers of the uterus and ovary**

**Note**

From high-density oligonucleotide microarrays and using quantitative real-time RT-PCR, ASPM is found more highly expressed in cancers of the uterus and ovary when compared with their normal endometrium counterparts.

**References**


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