

## Gene Section

### Review

# AIP (aryl hydrocarbon receptor interacting protein)

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## Identity

**Other names:** ARA9, FKBP16, FKBP37, SMTPHN, XAP-2, XAP2

**HGNC (Hugo):** AIP

**Location:** 11q13.2

## DNA/RNA

### Description

The AIP gene is located on Chromosome 11 at 67250505-67258579 (GRCh37/hg19). The AIP gene is composed of 6 exons and spans approximately 8.07 kb of genomic DNA.

### Transcription

AIP gene encodes a 1250bp mRNA transcript. No splice variants have been identified.

### Pseudogene

No pseudogene reported.

## Protein

### Description

AIP protein consists of 330 amino acids with a molecular weight of 37 kDa.

AIP belongs to the family of tetratricopeptide repeat (TPR) domain-containing proteins. It has three TPR-domains which are important for protein-protein interactions and an  $\alpha$  helix at the C-terminal region and a PPIase-like domain (FKBP-type) in the N-terminus.

### Expression

AIP is expressed ubiquitously and found in various human tissues such as: heart, brain, lung, placenta, kidney, skeletal muscle, mouth mucosa, exocrine

pancreas, salivary gland, stomach, parathyroid, tonsil, nerve, ovary, connective adipose tissue, spleen, thymus, prostate, testis, colon, leucocytes and pituitary (Kuzhandaivelu et al., 1996; Leontiou et al., 2008).

### Localisation

Cytoplasm and nucleus.

### Function

To date, several AIP interacting partners have been identified including HBV-X, EBNA-3, AhR, Hsp90, Hsc70, PDE4A5, PDE2A3, PPAR $\alpha$ , TR $\beta$ 1, G $\alpha$ 13, Gaq, TOMM20, RET, survivin and ER $\alpha$ , which may indicate that AIP is involved in various cellular pathways, however, the consequences of these interactions are not fully understood (Cai et al., 2011; Trivellin and Korbonits, 2011).

Clinical and functional data supports its role as a tumour suppressor gene. Loss of heterozygosity (LOH) is found in AIP mutation positive tumours. Our lab has previously shown that over-expression of wild-type AIP in human fibroblast and pituitary cell lines reduced cell proliferation compared with the empty vector control in vitro whereas the mutant AIP loses this ability compared to the wild-type AIP (Leontiou et al., 2008). AIP knockdown with siRNA also supports the tumour-suppressor role for AIP as it results in increased cell proliferation in GH3 cells (Heliövaara et al., 2009; Leontiou et al., 2008).

Homozygous deletion of AIP is embryonically lethal due to cardiovascular developmental abnormalities and erythropoietic failure (Kang et al., 2011; Lin et al., 2007), suggesting that AIP has a crucial role for cardiac development and for maintaining erythropoiesis in mice. Heterozygote deletion of the AIP gene lead to the development of growth hormone- and prolactin-secreting pituitary adenomas (Raitila et al., 2010).

AIP is a molecular co-chaperone protein. The most studied partner is the nuclear xenobiotic receptor AhR (aryl hydrocarbon receptor). AIP regulates its sub-cellular localization and degradation. AhR, also known as dioxin receptor is a ligand activated transcription factor found in the cytoplasm as part of a multiprotein complex with Hsp90 (Perdew, 1988), AIP (Carver and Bradfield, 1997; Meyer et al., 1998) and p23 (Kazlauskas et al., 1999). After binding to its ligand it is transported to the nucleus where it heterodimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT). This complex then binds to DNA recognition sequences known as xenobiotic inducible response elements (XREs/DREs/AHREs) within the promoter region of specific genes, leading to the transcription of xenobiotic-metabolizing enzymes. However, there is conflicting data regarding the role of AIP on AhR function. Some findings suggested that AIP has a role in stabilising unliganded AhR in the cytoplasm (LaPres et al., 2000; Meyer and Perdew, 1999; Nukaya et al., 2010), therefore AIP may play a positive role in AhR-mediated signalling. In contrast, other studies have suggested that AIP has a negative effect on AhR transcriptional activity (Hollingshead et al., 2004; Pollenz et al., 2006; Pollenz and Dougherty, 2005). AIP has other functions related to the other interacting partners but it is currently not known how lack of AIP leads to pituitary tumorigenesis.

### Homology

AIP shares 94% and 93% sequence identity with mouse and rat AIP respectively.

## Mutations

### Germinal

Germline mutations of AIP are associated with familial isolated pituitary adenoma (FIPA). Approximately 20% of FIPA families and 13% of sporadic young (<30 years) onset have somatotroph or lactotroph adenomas (Cazabat et al., 2007; Cazabat et al., 2012; Chahal et al., 2010; Daly et al., 2007; Leontiou et al., 2008; Tichomirowa et al., 2011; Vierimaa et al., 2006). Over 50 pathogenic mutations have been identified including deletions, insertions, segmental duplications, nonsense, missense, splice-site and promoter mutations, as well as large deletions of whole exons or the entire AIP gene. Mutations are present throughout the whole length of the gene and disrupt the protein. Sixty five percent of known AIP variants result in a truncated protein. The majority of the missense mutations are typically clustered around the C-terminal part of the protein, appeared to be crucial for its biological function (Ozfirat and Korbonits, 2010). The most common mutation is found at residue 304, a mutational 'hotspot' CpG site. Informations regarding AIP mutations and polymorphisms are available in a locus-specific mutation database, available at: <http://aip.fipapatient.org/>.

### Somatic

Somatic mutations in AIP have not been found to date in sporadic pituitary adenomas. Somatic mutations in AIP have been investigated in colorectal cancers, breast cancers, prostate tumours (Georgitsi et al., 2007) as well as endocrine tumours (thyroid lesions, adrenal lesions, carcinoids, parathyroid lesions, paragangliomas, pancreatic endocrine tumours and adenocarcinoids) but no somatic mutations were found (Raitila et al., 2007; Tichomirowa et al., 2011).

## Implicated in

### Familial isolated pituitary adenoma (FIPA) and simplex pituitary adenoma cases with germline AIP mutation

#### Note

Familial isolated pituitary adenoma (FIPA) is an autosomal dominant disease with incomplete penetrance. Heterozygote germline mutations have been identified in the aryl hydrocarbon receptor interacting protein (AIP) gene in 20% of FIPA families. FIPA has been characterised in >200 families. Most of the FIPA families with AIP mutations presented somatotropinomas or somatomammotropinomas followed by prolactinomas as well as non-functioning adenomas and very rarely corticotroph or thyrotropinomas. Approximately, eighty five percent of AIP mutation positive FIPA patients have acromegaly and around fifty percent with AIP mutation positive somatotropinomas are associated with gigantism (Daly et al., 2010). Pituitary tumours in AIP mutation positive patients have larger, more aggressive, invasive tumours, most commonly sparsely granulated subtype which show a poor response to somatostatin analogues (Daly et al., 2010) and also have a younger age at disease onset (18-24 years) (Korbonits and Kumar, 2012).

#### Prognosis

AIP mutation positive patients show younger mean age at diagnosis than sporadic pituitary cases. Decreased level of AIP has been correlated with tumour invasiveness in somatotropinomas (Kasuki Jomori de Pinho et al., 2011). Genetic screening is now able to stratify carrier subjects and help to diagnose the presymptomatic patients (Chahal et al., 2011).

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