Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Gene Section
Mini Review

ARNT (aryl hydrocarbon receptor nuclear translocator)

Oliver Hankinson

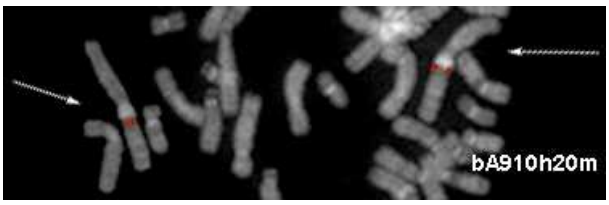
Department of Pathology and Laboratory Medicine, Jonsson Comprehensive Cancer Center, Center for Health Sciences, University of California, Los Angeles, CA 90095-1732, USA (OH)

Published in Atlas Database: October 2004

Online updated version : http://AtlasGeneticsOncology.org/Genes/ARNTID223ch1q21.html
DOI: 10.4267/2042/38129

Identity

Other names: HIF-1b
HGNC (Hugo): ARNT
Location: 1q21



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Note
The gene is about 65 kb in size and has 22 exons.

Transcription

Five alternative transcriptional start sites have been identified, located from 27 to 147 nucleotides 5' to the ATG translational initiation codon. There are two alternative polyadenylation sites, giving rise to transcripts of about 2600 and 4200 nucleotides. The 45 nucleotide exon 5 is an alternative exon and is spliced out in approximately half of the transcripts. This proportion does not seem to vary much between different tissues. No observable effects on the resulting protein due to omission of exon 5 have been noted. A transcript of about 1300 nucleotides is observed in some breast cancers and may be due to an alternative splicing event leading to elimination of the 3' end of the transcript.

Pseudogene

No pseudogenes for ARNT are known.

Protein

Description

The 87 kDa protein is comprised of 789 amino acids (if exon 5 is included) or 774 amino acids (if exon 5 is excluded).

Expression

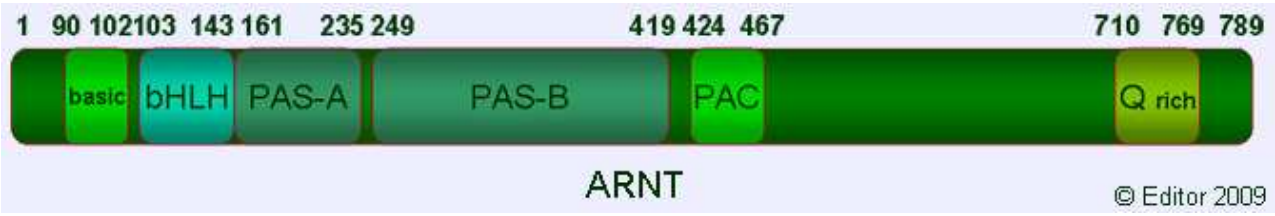
ARNT is expressed ubiquitously.

Localisation

ARNT is a nuclear protein in most cell types, although it may also be located in the cytosol, particularly during embryogenesis.

Function

ARNT serves as the dimerization partner for a number of other bHLH-PAS proteins, whose activity is modulated either by exogenous chemicals (the aryl hydrocarbon receptor (AHR)), or by hypoxia (hypoxia inducible factors 1, 2 and 3 alpha [HIF-1a, HIF-2a and HIF-3a), or which show restricted expression (e.g. SIM-1). The AHR/ARNT dimer activates transcription of several genes involved in metabolism of foreign chemicals, including CYP1A1, CYP1B1, and NADP(H): oxidoreductase (NQO1). Transcriptional activation of these genes depends upon prior binding of AHR to xenobiotic ligands, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) and benzo(a)pyrene. The AHR/ARNT dimer and ARNT itself can also impact signaling by the eostrogen receptor. The HIF-1a (and 2a and 3a) proteins are stabilized and activated by hypoxia (and hypoglycemia) and activate transcription of several genes involved in adapting to these adverse conditions,



bHLH, basic helix-loop-helix domain; PAS, Per/ARNT/Sim homology domain; A and B, the two approximately 50 amino-acid degenerative direct repeats within the PAS domain; Q-rich, glutamine-rich transactivation domain.

including the genes for erythropoietin (EPO), vascular endothelial growth factor (VEGF), and a number of enzymes of glycolysis. Unlike the AHR/ARNT and HIF/ARNT dimers, the SIM-1/ARNT dimer is probably not conditionally regulated. The above dimers bind specific DNA sequences in the regulatory regions of the responsive genes. The half-site for ARNT is on the 3' side of the recognition sequence and is 5'-GTG-3'. The sequence of the other half of the binding site depends upon the identity of the dimerization partner. DNA binding of ARNT is mediated by its basic region. There is evidence that the PAS region may also be involved. Dimerization between ARNT and other bHLH-PAS proteins is mediated by their HLH and PAS regions. The transcriptional activation domain of ARNT is located towards its carboxy terminus. ARNT appears capable of binding the E-box sequence 5'-CACGTG-3', although the affinity of ARNT for itself appears relatively low and no genes responsive to the homodimer have been identified.

Homology

Two ARNT-related genes, ARNT-2 and ARNT-3 (also called BMAL-1 or MOP3) have been identified. ARNT-2 is more restricted in expression than ARNT, but appears to dimerize with the same partner proteins as ARNT. ARNT-3 has a somewhat different dimerization potential than ARNT.

Mutations

Germinal

Several polymorphisms have been identified. None has shown an association with any disease.

Implicated in

Note

Involved in a t(1;12)(q21;p13) translocation with EVT6 fusion in acute myeloblastic leukemia.

Disease

Leukemia, Myelocytic, Acute AML-M2.

Prognosis

Unknown.

Hybrid/Mutated gene

Amino-terminal half of TEL fused to the complete coding sequence of ARNT except for its 8 amino-terminal amino acids. The reciprocal translocation probably contributes little if at all to the cancer phenotype.

References

Hoffman EC, Reyes H, Chu FF, Sander F, Conley LH, Brooks BA, Hankinson O. Cloning of a factor required for activity of the Ah (dioxin) receptor. Science. 1991 May 17;252(5008):954-8

Reyes H, Reisz-Porszasz S, Hankinson O. Identification of the Ah receptor nuclear translocator protein (Arnt) as a component of the DNA binding form of the Ah receptor. Science. 1992 May 22;256(5060):1193-5

Johnson B, Brooks BA, Heinzmann C, Diep A, Mohandas T, Sparkes RS, Reyes H, Hoffman E, Lange E, Gatti RA. The Ah receptor nuclear translocator gene (ARNT) is located on q21 of human chromosome 1 and on mouse chromosome 3 near Cf-3. Genomics. 1993 Sep;17(3):592-8

Reisz-Porszasz S, Probst MR, Fukunaga BN, Hankinson O. Identification of functional domains of the aryl hydrocarbon receptor nuclear translocator protein (ARNT). Mol Cell Biol. 1994 Sep;14(9):6075-86

Bacsi SG, Reisz-Porszasz S, Hankinson O. Orientation of the heterodimeric aryl hydrocarbon (dioxin) receptor complex on its asymmetric DNA recognition sequence. Mol Pharmacol. 1995 Mar;47(3):432-8

Swanson HI, Chan WK, Bradfield CA. DNA binding specificities and pairing rules of the Ah receptor, ARNT, and SIM proteins. J Biol Chem. 1995 Nov 3;270(44):26292-302

Wang GL, Jiang BH, Rue EA, Semenza GL. Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O2 tension. Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5510-4

Wood SM, Gleadle JM, Pugh CW, Hankinson O, Ratcliffe PJ. The role of the aryl hydrocarbon receptor nuclear translocator (ARNT) in hypoxic induction of gene expression. Studies in ARNT-deficient cells. J Biol Chem. 1996 Jun 21;271(25):15117-23

Kozak KR, Abbott B, Hankinson O. ARNT-deficient mice and placental differentiation. Dev Biol. 1997 Nov 15;191(2):297-305

Maltepe E, Schmidt JV, Baunoch D, Bradfield CA, Simon MC. Abnormal angiogenesis and responses to glucose and oxygen deprivation in mice lacking the protein ARNT. Nature. 1997 Mar 27;386(6623):403-7

Sun W, Zhang J, Hankinson O. A mutation in the aryl hydrocarbon receptor (AHR) in a cultured mammalian cell line identifies a novel region of AHR that affects DNA binding. J Biol Chem. 1997 Dec 12;272(50):31845-54

Wilson CL, Thomsen J, Hoivik DJ, Wormke MT, Stanker L, Holtzapple C, Safe SH. Aryl hydrocarbon (Ah) nonresponsiveness in estrogen receptor-negative MDA-MB-231 cells is associated with expression of a variant arnt protein. Arch Biochem Biophys. 1997 Oct 1;346(1):65-73

Salomon-Nguyen F, Della-Valle V, Mauchauffe M, Busson-Le Coniat M, Ghysdael J, Berger R, Bernard OA. The t(1;12)(q21;p13) translocation of human acute myeloblastic leukemia results in a TEL-ARNT fusion. Proc Natl Acad Sci U S A. 2000 Jun 6;97(12):6757-62

Scheel J, Schrenk D. Genomic structure of the human Ah receptor nuclear translocator gene (hARNT). Hum Genet. 2000 Oct;107(4):397-9

Keith B, Adelman DM, Simon MC. Targeted mutation of the murine arylhydrocarbon receptor nuclear translocator 2 (Arnt2) gene reveals partial redundancy with Arnt. Proc Natl Acad Sci U S A. 2001 Jun 5;98(12):6692-7

Beischlag TV, Wang S, Rose DW, Torchia J, Reisz-Porszasz S, Muhammad K, Nelson WE, Probst MR, Rosenfeld MG, Hankinson O. Recruitment of the NCoA/SRC-1/p160 family of transcriptional coactivators by the aryl hydrocarbon receptor/aryl hydrocarbon receptor nuclear translocator complex. Mol Cell Biol. 2002 Jun;22(12):4319-33

Scheel J, Hussong R, Schrenk D, Schmitz HJ. Variability of the human aryl hydrocarbon receptor nuclear translocator (ARNT) gene. J Hum Genet. 2002;47(5):217-24

Tojo M, Matsuzaki K, Minami T, Honda Y, Yasuda H, Chiba T, Saya H, Fujii-Kuriyama Y, Nakao M. The aryl hydrocarbon receptor nuclear transporter is modulated by the SUMO-1 conjugation system. J Biol Chem. 2002 Nov 29;277(48):46576-85

Brunnberg S, Pettersson K, Rydin E, Matthews J, Hanberg A, Pongratz I. The basic helix-loop-helix-PAS protein ARNT functions as a potent coactivator of estrogen receptor-dependent transcription. Proc Natl Acad Sci U S A. 2003 May 27;100(11):6517-22

Ohtake F, Takeyama K, Matsumoto T, Kitagawa H, Yamamoto Y, Nohara K, Tohyama C, Krust A, Mimura J, Chambon P, Yanagisawa J, Fujii-Kuriyama Y, Kato S. Modulation of oestrogen receptor signalling by association with the activated dioxin receptor. Nature. 2003 May 29;423(6939):545-50

Takagi S, Tojo H, Tomita S, Sano S, Itami S, Hara M, Inoue S, Horie K, Kondoh G, Hosokawa K, Gonzalez FJ, Takeda J. Alteration of the 4-sphingenine scaffolds of ceramides in keratinocyte-specific Arnt-deficient mice affects skin barrier function. J Clin Invest. 2003 Nov;112(9):1372-82

Beischlag TV, Taylor RT, Rose DW, Yoon D, Chen Y, Lee WH, Rosenfeld MG, Hankinson O. Recruitment of thyroid hormone receptor/retinoblastoma-interacting protein 230 by the aryl hydrocarbon receptor nuclear translocator is required for the transcriptional response to both dioxin and hypoxia. J Biol Chem. 2004 Dec 24;279(52):54620-8

Walisser JA, Bunger MK, Glover E, Harstad EB, Bradfield CA. Patent ductus venosus and dioxin resistance in mice harboring a hypomorphic Arnt allele. J Biol Chem. 2004 Apr 16;279(16):16326-31

This article should be referenced as such:

Hankinson O. ARNT (aryl hydrocarbon receptor nuclear translocator). Atlas Genet Cytogenet Oncol Haematol. 2004; 8(4):313-315.