

# Gene Section

## Review

# IRS1 (insulin receptor substrate 1)

João Agostinho Machado-Neto, Fabiola Traina

Hematology and Hemotherapy Center-University of Campinas/Hemocentro-Unicamp, Instituto Nacional de Ciencia e Tecnologia do Sangue, Campinas, Sao Paulo, Brazil (JAMN), Hematology and Hemotherapy Center-University of Campinas/Hemocentro-Unicamp, Instituto Nacional de Ciencia e Tecnologia do Sangue, Campinas, Sao Paulo, Brazil and Hematology/Oncology Division, Department of Internal Medicine, Medical School of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil (FT)

Published in Atlas Database: March 2013

Online updated version : <http://AtlasGeneticsOncology.org/Genes/IRS1ID384ch2q36.html>

DOI: 10.4267/2042/51422

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## Identity

**Other names:** HIRS-1

**HGNC (Hugo):** IRS1

**Location:** 2q36.3

## DNA/RNA

### Note

Insulin receptor substrate 1 (IRS1) was the first IRS family member to be identified and cloned (Sun et al., 1991).

The entire gene is about 68,4 kb and contains 2 exons (start: 227596033 and end: 227664745; orientation: minus strand). The cDNA contains 8743 bp.

## Protein

### Description

IRS1 belongs to the insulin receptor substrate (IRS) protein family, these proteins are characterized by the presence of a pleckstrin homology (PH) domain and a phosphotyrosine binding (PTB) domain (figure 1).

The PH domain contributes to protein-protein binding and facilitates the recruitment of IRS proteins by cell membrane receptors. The PTB domain is activated by receptors (Mardilovich et al., 2009).

### Expression

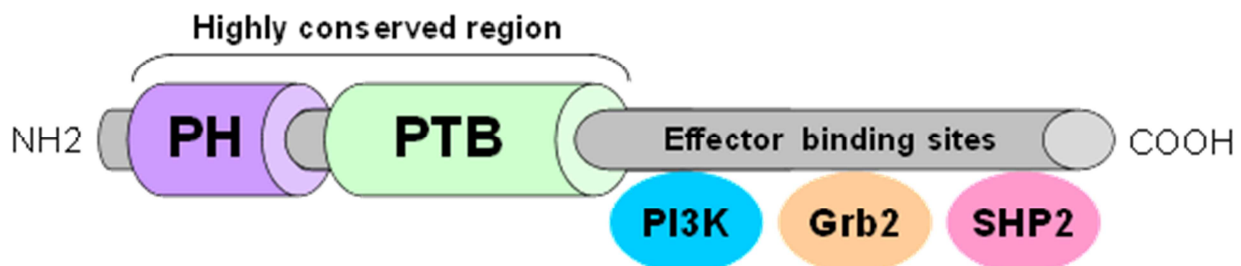
Ubiquitous.

### Localisation

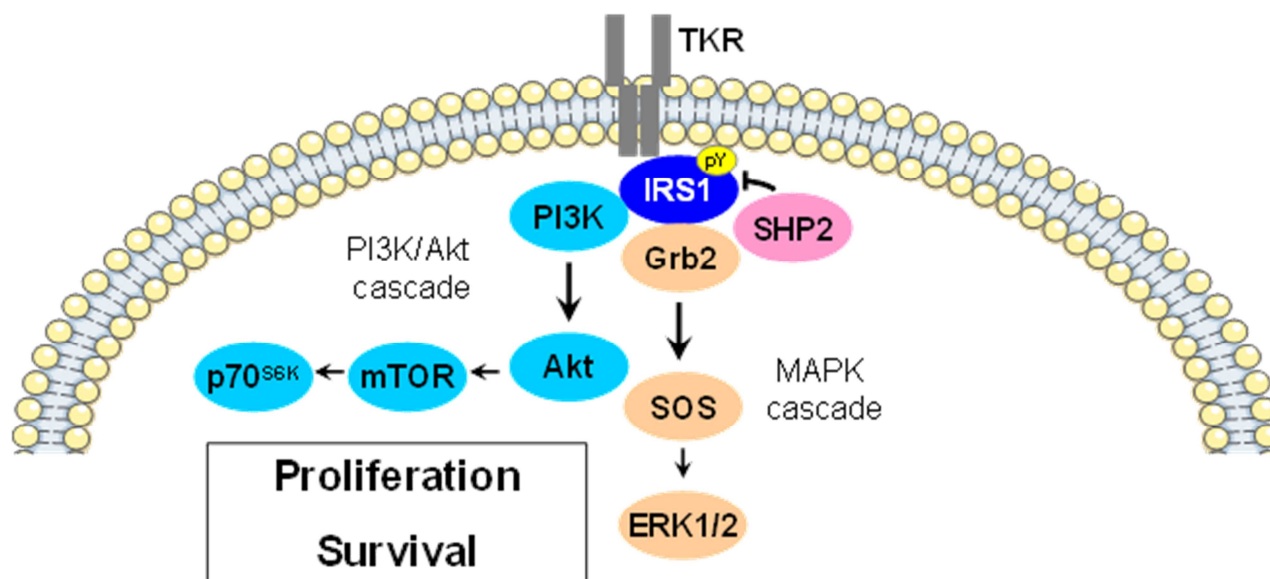
IRS1 is predominantly found in the cytoplasm. Nuclear localization may occur in some cell types and under specific stimuli.

### Function

IRS1 is an intracellular signaling adaptor protein that integrates and coordinates numerous biologically key extracellular signals within the cell. First identified as a signaling intermediate of the insulin receptor (IR), it is now clear that IRS1 is the main substrate of the insulin-like growth factor 1 receptor (IGF1R) (Dearth et al., 2007).



**Figure 1. Schematic structure of IRS1.** Interaction domains of IRS1: pleckstrin homology (PH) domain (purple), phosphotyrosine binding (PTB) domain (green) and effector binding sites (including PI3K, Grb2 and SHP2) are indicated.



**Figure 2. IRS1 signaling pathway.** IRS1 is recruited by its PH/PTB domains and phosphorylated in tyrosine residues (pY) by upstream tyrosine kinase receptors. Tyrosine phosphorylated IRS1 binds to signaling effectors and activates signaling cascades, regulating several biological processes, including proliferation and survival.

IRS1 contains multiple tyrosine phosphorylation sites, which during insulin stimulation are phosphorylated and act as docking sites for multiple SH2-containing proteins including PI3K, Grb2, Nck, Crk, Fyn, Syp and SHP2 (Mardilovich et al., 2009).

The two best-studied being the PI3K/Akt/mTOR and the MAPK pathway, which includes the ERK protein (figure 2) (Mardilovich et al., 2009). IRS1 has no intrinsic kinase activity and requires upstream activators, however many studies have shown that this signaling adaptor is in itself oncogenic and can induce malignant transformation (Dearth et al., 2007).

More recently, nuclear localization of IRS1 was observed in cells expressing SV40 T antigen, fibroblasts under IGF1 stimulation, hepatocytes, 32D cells and others.

Several nuclear functions have been attributed to IRS1, including DNA repair fidelity, transcriptional activity and cell growth, which contributes to tumor development and progression (Reiss et al., 2011).

### Homology

IRS1 shares high homology in its N-termini with the other members of the IRS proteins family.

IRS1 also shares a high homology among different species (table 1).

## Mutations

### Note

Mutations in this gene are associated with type II diabetes and susceptibility to insulin resistance (Kovacs et al., 2003).

## Implicated in

### *Philadelphia chromosome-positive (Ph+) leukemias*

### Note

IRS1 was identified as a binding partner of BCR-ABL protein and found to be involved in the activation of the PI3K/Akt/mTOR and MAPK signaling pathway in the BCR-ABL network (Traina et al., 2003).

In BCR-ABL positive leukemia cells, IRS1 silencing resulted in decreased cell proliferation and clonogenicity (Machado-Neto et al., 2011).

% Identity for: <i>Homo sapiens</i> IRS1	Symbol	Protein	DNA
vs. <i>P. troglodytes</i>	IRS1	99.4	99.6
vs. <i>M. mulatta</i>	IRS4	98.5	97.3
vs. <i>C. lupus</i>	IRS1	92.2	89.2
vs. <i>B. taurus</i>	IRS1	91.6	89.0
vs. <i>M. musculus</i>	Irs1	90.5	85.9
vs. <i>R. norvegicus</i>	Irs1	90.6	85.7
vs. <i>G. gallus</i>	IRS1	91.4	92.8
vs. <i>D. rerio</i>	Irs1	65.5	61.7

**Table 1. Comparative identity of human IRS1 with other species.** Source: HomoloGene.

In addition, IRS1 expression was found to be negatively correlated with survival in patients with Ph+ acute lymphoblastic leukemia, regardless of age and white blood cell count at diagnosis (Juric et al., 2007).

### **Breast cancer**

#### **Note**

In breast cancer tumors, IRS1 has been described as constitutively activated and its expression has been correlated with poor differentiation and positive lymph node status (Chang et al., 2002; Lee et al., 1999; Koda et al., 2005). High levels of IRS1 were associated with lower disease-free survival and positively correlated with proliferation in estrogen receptor (ER) positive breast cancer tumors (Rocha et al., 1997). In ER positive breast cancer cells, IRS1 silencing promoted apoptosis and increased the sensibility to chemotherapy (Cesarone et al., 2006).

### **Hepatocellular carcinoma**

#### **Note**

IRS1 was found overexpressed in 80% of hepatocellular carcinoma (HCC) when compared with adjacent HCC-free tissue (Cantarini et al., 2006). In vitro experiments provided evidence that IRS1 overexpression was able to promote malignant transformation of hepatocytes (Tanaka et al., 1997).

### **Lung cancer**

#### **Note**

Han et al. reported a downregulation of IRS1 in non-small cell lung cancer (NSCLC) and suggested that loss of IRS1 might be an early event in NSCLC development (Han et al., 2006).

### **Medulloblastoma**

#### **Note**

Abundant IRS1 expression was found in medulloblastoma cell lines and medulloblastoma biopsies. Nuclear translocation of IRS1 was observed in all cell lines and primary samples in the presence of

the JC virus T antigen (Del Valle et al., 2002).

### **Mesothelioma**

#### **Note**

Up-regulation of IRS1 was found in mesothelioma samples and may contribute to malignant pleural mesothelioma tumorigenesis by IGF1-induced cell proliferation (Hoang et al., 2004).

### **Ovarian cancer**

#### **Note**

The majority of malignant epithelial ovarian tumors showed IRS1 overexpression when compared with normal ovarian tissue, suggesting a correlation between IRS1 expression and cancer phenotype. The same study suggested that IRS1 is an important growth-regulatory protein and may be a possible target in ovarian cancer (Ravikumar et al., 2007).

### **Pancreatic cancer**

#### **Note**

IRS1 was highly expressed in 43% of pancreatic cancer samples when compared with normal pancreas samples (Bergmann et al., 1996).

### **Prostate cancer**

#### **Note**

High expression of IRS1 was correlated with high expression of IGF1R in both benign and malignant prostate samples (Hellowell et al., 2002), but IRS1 expression did not differ among these samples. In prostate cancer cells, IRS1 silencing plus rapamycin treatment synergistically antagonized the activation of mTOR and induced tumor suppression in vivo, through inhibition of proliferation and induction of apoptosis (Oliveira et al., 2008).

### **Endometrial cancer**

#### **Note**

IRS1 activation was significantly elevated in patients with endometrial cancer (EC) compared to those

without EC and was associated with aggressive features. In addition, Wang et al. suggested that the inhibition of the IR/IRS1/PI3K/Akt pathway could be used as preventive and therapeutic strategies for EC (Wang et al., 2012).

## Colorectal cancer

### Note

Esposito et al. reported that IRS1 was found highly expressed in adenomas of familial adenomatous polyposis patients, relative to paired normal mucosa, and in metastasized colorectal tumors compared with primary colorectal cancer (CRC) and colonic epithelium (Esposito et al., 2012). The authors also related that IRS1 staining was associated with high expressions of Ki67, p53, and  $\beta$ -catenin, suggesting that IRS1 is modulated according to CRC differentiation and plays a role in CRC progression and metastasis (Esposito et al., 2012).

## To be noted

### Note

Animal model: IRS1 knockout mice were born alive but were showed retarded embryonic and postnatal growth (approximately 30% smaller than wild type littermates), and also had resistance to the glucose-lowering effects of insulin, IGF1 and IGF2 (Tamemoto et al., 1994).

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*This article should be referenced as such:*

Machado-Neto JA, Traina F. IRS1 (insulin receptor substrate 1). *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(9):594-598.

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