Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

# Gene Section
## Review

# STAT5B (signal transducer and activator of transcription 5B)

**Amanda M Del Rosario, Teresa M Bernaciak, Corinne M Silva**

Department of Biological Engineering, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA (AMDR), NIAID/NIH/DHHS, 6610 Rockledge Drive, Bethesda, MD 20817, USA (TMB), DEM/NIDDK/NIH, 6707 Democracy Blvd, Bethesda, MD 20892, USA (CMS)

Published in Atlas Database: August 2011

Online updated version : http://AtlasGeneticsOncology.org/Genes/STAT5BID217ch17q21.html
DOI: 10.4267/2042/46938



## Identity

**Other names:** STAT5

**HGNC (Hugo):** STAT5B

**Location:** 17q21.2

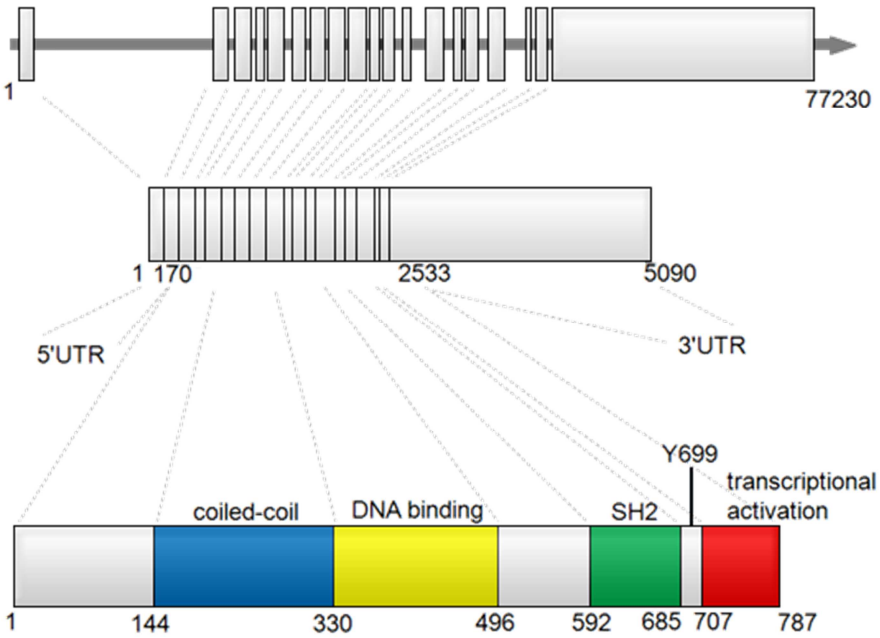
## DNA/RNA

### *Description*

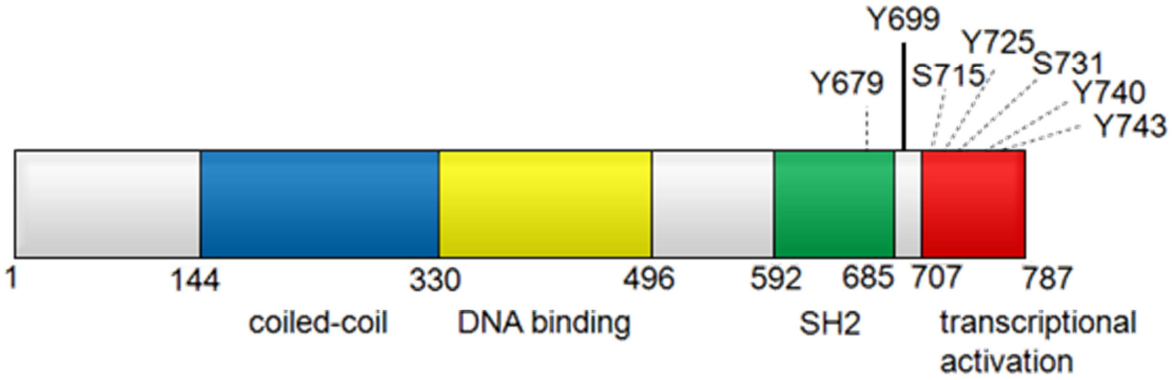
The STAT5b gene is composed of 77229 base pairs and contains 19 exons. As exon 1 contains only the 5' UTR, there are 18 coding exons. The mRNA is composed of 5090 base pairs.

### *Transcription*

There is one major transcript.




**The STAT5b gene.** The STAT5b gene is composed of 19 exons that are transcribed as a 5090 nucleotide RNA transcript. The RNA is translated into the STAT5b protein containing 787 amino acids.




**Schematic of the STAT5b protein.** The STAT5b protein contains several conserved domains: the coiled-coil domain, the DNA binding domain, the SH2 domain, and the carboxy-terminal transactivation domain. While phosphorylation of Y699 is required for transcriptional activity, there are multiple tyrosine and serine phosphorylation sites that have been identified under specific conditions and in certain cell types.

# Protein

**Note**

STAT5b is composed of 787 amino acids (92 kD).

## *Description*

STAT5b is a member of the signal transducer and activator of transcription (STAT) family. The STAT proteins contain several conserved domains: the coiled-coil domain, the DNA binding domain, the SH2 domain, and the carboxy-terminal transactivation domain. STATs remain latent in the cytoplasm until the binding of a cytokine or growth factor to its receptor, resulting in recruitment of the STAT to the ligand receptor complex (Levy and Darnell, 2002; Herrington et al., 1999; Heim et al., 1995). The STAT protein is then phosphorylated by receptor tyrosine kinases or non-receptor tyrosine kinases, such as Janus kinases (JAKs) and Src family members. This phosphorylation results in SH2 domain mediated dimerization of STATs and their translocation to the nucleus. In the nucleus, STAT dimers bind to consensus DNA sequences and recruit additional transcription machinery to initiate specific gene regulation. To date, seven members of the STAT family have been identified (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) (Silva, 2004; Calò et al., 2003; Moriggl et al., 1996; Liu et al., 1996; Liu et al., 1997).

STAT5b is activated by a variety of stimuli, including interleukins, erythropoietin, growth hormone (GH), prolactin (Prl), and epidermal growth factor (EGF). Activation of STAT5b results in phosphorylation of tyrosine 699. Phosphorylation of this tyrosine is required for DNA binding and transcriptional activity. Mutation of Y699 of STAT5b inhibits stimulant-induced tyrosine phosphorylation, DNA binding, and transcriptional activity (Gebert et al., 1997; Gouilleux et al., 1994; Kloth et al., 2003). Additional tyrosine phosphorylation sites (Y679, Y725, Y740, and Y743) and serine phosphorylation sites (S715, S731) have been shown to alter STAT5b transcriptional activity (Kloth et al., 2002; Weaver and Silva, 2006; Yamashita et al., 2001; Park et al., 2001; Decker and Kovarik, 2000).

While no classic nuclear localization signal (NLS) composed of a cluster of basic amino acids has been reported for the STAT5b, the STAT5b dimer is actively translocated through the nuclear pore complex and accumulates in the nucleus upon phosphorylation (Xu and Massagué, 2004).

STAT5b can be negatively regulated by phosphatase-mediated dephosphorylation, ubiquitination-promoting proteosome degradation, or by negative feedback loops.

## *Expression*

Ubiquitous.

## *Localisation*

STAT5b is localized in the cytoplasm and translocates to the nucleus upon phosphorylation of Y699. However, unphosphorylated STAT5b has also been reported to be found in the nucleus (Brown and Zeidler, 2008; Iyer and Reich, 2008; Zeng et al., 2002).

## *Function*

Transcription factor. STAT5b mediates the transcription of numerous genes in various cell signaling pathways involved in cellular proliferation, differentiation, and cell survival. The STATs bind TTC(N3)GAA gamma-interferon-activating sequence (GAS) sites in the promoters of target genes.

## *Homology*

Shares homology with the other STAT family members (STAT1, 2, 3, 4, 5a, and 6). Additionally, STAT5a and STAT5b are 94% similar at the amino acid level, differing primarily at the C-terminus (Teglund et al., 1998; Silva et al., 1996; Lin et al., 1996; Liu et al., 1995).

# Mutations

**Note**

To date, there are 6 reported cases of humans having a mutant STAT5b, and these cases result from five

different STAT5b mutations. The first STAT5b mutation in a human to be reported was the A630P STAT5b mutant. This single point mutation in the SH2 domain causes missfolding of STAT5b. A nonsense mutation in the coiled-coil domain (R152X) results in the absence of detectable STAT5b protein. Insertion of a nucleotide in the DBD at position 1102 (Q368fsX376) or 1191 (N398E) causes a frameshift mutation resulting in a non-functional truncated STAT5b. Likewise, a single nucleotide deletion in the linker domain at position 1680 (E561R) also results in a truncated STAT5b. In each of the 6 cases, STAT5b protein is not detectable, but STAT5a protein levels are unchanged. These reports are from homozygous patients while the parents are heterozygous for the STAT5b mutation and display a normal phenotype. The phenotype of each STAT5b mutant is similar: pronounced short stature, growth hormone insensitivity despite normal to high levels of GH in the serum, and extremely low IGF-I and IGFBP-3 levels (Chia et al., 2006; Hwa et al., 2007; Nadeau et al., 2011).

# Implicated in

## *Solid tumors*

**Note**

STAT5b is implicated in prostate cancer (Koptyra et al., 2011; Clevenger, 2004), breast cancer (Bernaciak et al., 2009; Peck et al., 2011; Strauss et al., 2006; Sultan et al., 2005; Yamashita et al., 2003), lung cancer (Sánchez-Ceja et al., 2006), head and neck cancer (Koppikar et al., 2008), ovarian cancer (Chen et al., 2004), hepatocellular carcinoma (Lee et al., 2006), cervical cancer (Lopez et al., 2011), and colorectal cancer (Du et al., 2011).

## *Leukemias and lymphomas*

**Note**

STAT5b is involved in the proliferation of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) cells (Baśkiewicz-Masiuk and Machalińkski, 2004; Sternberg and Gilliland, 2004; Hoover et al., 2001; de Groot et al., 1999). Additionally, STAT5b has been found to fuse with the retinoic acid receptor-alpha (RARalpha) gene in a subset of acute promyelocytic leukemias (APLL) (Arnould et al., 1999). Furthermore, STAT5b plays a role in the development of lymphoblastic lymphoma (Bessette et al., 2008; Nieborowska-Skorska et al., 2001).

## *Laron type dwarfism II*

**Note**

Laron type dwarfism II (LTD2) is mediated by defects in STAT5b (Nadeau et al., 2011; Freeth et al., 1998; Chia et al., 2006).

## *Graft-versus-host disease*

**Note**

Constitutively active STAT5b increases expansion of regulatory T cells (Treg), and these Tregs are more potent suppressors of graft-versus-host disease in vivo, compared to wild-type Tregs (Vogtenhuber et al., 2010).

## *Crohn's disease/colitis*

**Note**

Growth hormone reduces mucosal inflammation in colitis by activating STAT5b, such that STAT5b deficient mice demonstrated more severe colitis compared to wild-type mice (Han et al., 2006).

## *Diabetes and metabolic disorder*

**Note**

Upon leptin stimulation, the leptin receptor can mediate STAT5b tyrosine phosphorylation and transcriptional activity in the liver, gastrointestinal tract, and brain (Mütze et al., 2007; Ghilardi et al., 1996; Gong et al., 2007).

# References

Gouilleux F, Wakao H, Mundt M, Groner B. Prolactin induces phosphorylation of Tyr694 of Stat5 (MGF), a prerequisite for DNA binding and induction of transcription. EMBO J. 1994 Sep 15;13(18):4361-9

Heim MH, Kerr IM, Stark GR, Darnell JE Jr. Contribution of STAT SH2 groups to specific interferon signaling by the Jak-STAT pathway. Science. 1995 Mar 3;267(5202):1347-9

Liu X, Robinson GW, Gouilleux F, Groner B, Hennighausen L. Cloning and expression of Stat5 and an additional homologue (Stat5b) involved in prolactin signal transduction in mouse mammary tissue. Proc Natl Acad Sci U S A. 1995 Sep 12;92(19):8831-5

Ghilardi N, Ziegler S, Wiestner A, Stoffel R, Heim MH, Skoda RC. Defective STAT signaling by the leptin receptor in diabetic mice. Proc Natl Acad Sci U S A. 1996 Jun 25;93(13):6231-5

Lin JX, Mietz J, Modi WS, John S, Leonard WJ. Cloning of human Stat5B. Reconstitution of interleukin-2-induced Stat5A and Stat5B DNA binding activity in COS-7 cells. J Biol Chem. 1996 May 3;271(18):10738-44

Liu X, Robinson GW, Hennighausen L. Activation of Stat5a and Stat5b by tyrosine phosphorylation is tightly linked to mammary gland differentiation. Mol Endocrinol. 1996 Dec;10(12):1496-506

Moriggl R, Gouilleux-Gruart V, Jähne R, Berchtold S, Gartmann C, Liu X, Hennighausen L, Sotiropoulos A, Groner B, Gouilleux F. Deletion of the carboxyl-terminal transactivation domain of MGF-Stat5 results in sustained DNA binding and a dominant negative phenotype. Mol Cell Biol. 1996 Oct;16(10):5691-700

Silva CM, Lu H, Day RN. Characterization and cloning of STAT5 from IM-9 cells and its activation by growth hormone. Mol Endocrinol. 1996 May;10(5):508-18

Gebert CA, Park SH, Waxman DJ. Regulation of signal transducer and activator of transcription (STAT) 5b activation by the temporal pattern of growth hormone stimulation. Mol Endocrinol. 1997 Apr;11(4):400-14

Liu X, Robinson GW, Wagner KU, Garrett L, Wynshaw-Boris A, Hennighausen L. Stat5a is mandatory for adult mammary gland development and lactogenesis. Genes Dev. 1997 Jan 15;11(2):179-86

Freeth JS, Silva CM, Whatmore AJ, Clayton PE. Activation of the signal transducers and activators of transcription signaling pathway by growth hormone (GH) in skin fibroblasts from normal and GH binding protein-positive Laron Syndrome children. Endocrinology. 1998 Jan;139(1):20-8

Teglund S, McKay C, Schuetz E, van Deursen JM, Stravopodis D, Wang D, Brown M, Bodner S, Grosveld G, Ihle JN. Stat5a and Stat5b proteins have essential and nonessential, or redundant, roles in cytokine responses. Cell. 1998 May 29;93(5):841-50

de Groot RP, Raaijmakers JA, Lammers JW, Jove R, Koenderman L. STAT5 activation by BCR-Abl contributes to transformation of K562 leukemia cells. Blood. 1999 Aug 1;94(3):1108-12

Herrington J, Rui L, Luo G, Yu-Lee LY, Carter-Su C. A functional DNA binding domain is required for growth hormone-induced nuclear accumulation of Stat5B. J Biol Chem. 1999 Feb 19;274(8):5138-45

Yamashita H, Nevalainen MT, Xu J, LeBaron MJ, Wagner KU, Erwin RA, Harmon JM, Hennighausen L, Kirken RA, Rui H. Role of serine phosphorylation of Stat5a in prolactin-stimulated beta-casein gene expression. Mol Cell Endocrinol. 2001 Oct 25;183(1-2):151-63

Arnould C, Philippe C, Bourdon V, Gr goire MJ, Berger R, Jonveaux P. The signal transducer and activator of transcription STAT5b gene is a new partner of retinoic acid receptor alpha in acute promyelocytic-like leukaemia. Hum Mol Genet. 1999 Sep;8(9):1741-9

Decker T, Kovarik P. Serine phosphorylation of STATs. Oncogene. 2000 May 15;19(21):2628-37

Hoover RR, Gerlach MJ, Koh EY, Daley GQ. Cooperative and redundant effects of STAT5 and Ras signaling in BCR/ABL transformed hematopoietic cells. Oncogene. 2001 Sep 13;20(41):5826-35

Nieborowska-Skorska M, Slupianek A, Xue L, Zhang Q, Raghunath PN, Hoser G, Wasik MA, Morris SW, Skorski T. Role of signal transducer and activator of transcription 5 in nucleophosmin/ anaplastic lymphoma kinase-mediated malignant transformation of lymphoid cells. Cancer Res. 2001 Sep 1;61(17):6517-23

Park SH, Yamashita H, Rui H, Waxman DJ. Serine phosphorylation of GH-activated signal transducer and activator of transcription 5a (STAT5a) and STAT5b: impact on STAT5 transcriptional activity. Mol Endocrinol. 2001 Dec;15(12):2157-71

Kloth MT, Catling AD, Silva CM. Novel activation of STAT5b in response to epidermal growth factor. J Biol Chem. 2002 Mar 8;277(10):8693-701

Levy DE, Darnell JE Jr. Stats: transcriptional control and biological impact. Nat Rev Mol Cell Biol. 2002 Sep;3(9):651-62

Zeng R, Aoki Y, Yoshida M, Arai K, Watanabe S. Stat5B shuttles between cytoplasm and nucleus in a cytokine-dependent and -independent manner. J Immunol. 2002 May 1;168(9):4567-75

Calò V, Migliavacca M, Bazan V, Macaluso M, Buscemi M, Gebbia N, Russo A. STAT proteins: from normal control of cellular events to tumorigenesis. J Cell Physiol. 2003 Nov;197(2):157-68

Kloth MT, Laughlin KK, Biscardi JS, Boerner JL, Parsons SJ, Silva CM. STAT5b, a Mediator of Synergism between c-Src and the Epidermal Growth Factor Receptor. J Biol Chem. 2003 Jan 17;278(3):1671-9

Yamashita H, Iwase H, Toyama T, Fujii Y. Naturally occurring dominant-negative Stat5 suppresses transcriptional activity of estrogen receptors and induces apoptosis in T47D breast cancer cells. Oncogene. 2003 Mar 20;22(11):1638-52

Baśkiewicz-Masiuk M, Machaliński B. The role of the STAT5 proteins in the proliferation and apoptosis of the CML and AML cells. Eur J Haematol. 2004 Jun;72(6):420-9

Chen H, Ye D, Xie X, Chen B, Lu W. VEGF, VEGFRs expressions and activated STATs in ovarian epithelial carcinoma. Gynecol Oncol. 2004 Sep;94(3):630-5

Clevenger CV. Roles and regulation of stat family transcription factors in human breast cancer. Am J Pathol. 2004 Nov;165(5):1449-60

Silva CM. Role of STATs as downstream signal transducers in Src family kinase-mediated tumorigenesis. Oncogene. 2004 Oct 18;23(48):8017-23

Sternberg DW, Gilliland DG. The role of signal transducer and activator of transcription factors in leukemogenesis. J Clin Oncol. 2004 Jan 15;22(2):361-71

Xu L, Massagué J. Nucleocytoplasmic shuttling of signal transducers. Nat Rev Mol Cell Biol. 2004 Mar;5(3):209-19

Sultan AS, Xie J, LeBaron MJ, Ealley EL, Nevalainen MT, Rui H. Stat5 promotes homotypic adhesion and inhibits invasive characteristics of human breast cancer cells. Oncogene. 2005 Jan 27;24(5):746-60

Chia DJ, Subbian E, Buck TM, Hwa V, Rosenfeld RG, Skach WR, Shinde U, Rotwein P. Aberrant folding of a mutant Stat5b causes growth hormone insensitivity and proteasomal dysfunction. J Biol Chem. 2006 Mar 10;281(10):6552-8

Han X, Osuntokun B, Benight N, Loesch K, Frank SJ, Denson LA. Signal transducer and activator of transcription 5b promotes mucosal tolerance in pediatric Crohn's disease and murine colitis. Am J Pathol. 2006 Dec;169(6):1999-2013

Lee TK, Man K, Poon RT, Lo CM, Yuen AP, Ng IO, Ng KT, Leonard W, Fan ST. Signal transducers and activators of transcription 5b activation enhances hepatocellular carcinoma aggressiveness through induction of epithelial-mesenchymal transition. Cancer Res. 2006 Oct 15;66(20):9948-56

Sánchez-Ceja SG, Reyes-Maldonado E, Vázquez-Manríquez ME, López-Luna JJ, Belmont A, Gutiérrez-Castellanos S. Differential expression of STAT5 and Bcl-xL, and high expression of Neu and STAT3 in non-small-cell lung carcinoma. Lung Cancer. 2006 Nov;54(2):163-8

Strauss BL, Bratthauer GL, Tavassoli FA. STAT 5a expression in the breast is maintained in secretory carcinoma, in contrast to other histologic types. Hum Pathol. 2006 May;37(5):586-92

Weaver AM, Silva CM. Modulation of signal transducer and activator of transcription 5b activity in breast cancer cells by mutation of tyrosines within the transactivation domain. Mol Endocrinol. 2006 Oct;20(10):2392-405

Gong Y, Ishida-Takahashi R, Villanueva EC, Fingar DC, Münzberg H, Myers MG Jr. The long form of the leptin receptor regulates STAT5 and ribosomal protein S6 via alternate mechanisms. J Biol Chem. 2007 Oct 19;282(42):31019-27

Hwa V, Camacho-Hübner C, Little BM, David A, Metherell LA, El-Khatib N, Savage MO, Rosenfeld RG. Growth hormone insensitivity and severe short stature in siblings: a novel mutation at the exon 13-intron 13 junction of the STAT5b gene. Horm Res. 2007;68(5):218-24

Mütze J, Roth J, Gerstberger R, Hübschle T. Nuclear translocation of the transcription factor STAT5 in the rat brain after systemic leptin administration. Neurosci Lett. 2007 May 7;417(3):286-91

Bessette K, Lang ML, Fava RA, Grundy M, Heinen J, Horne L, Spolski R, Al-Shami A, Morse HC 3rd, Leonard WJ, Kelly JA. A Stat5b transgene is capable of inducing CD8+ lymphoblastic lymphoma in the absence of normal TCR/MHC signaling. Blood. 2008 Jan 1;111(1):344-50

Brown S, Zeidler MP. Unphosphorylated STATs go nuclear. Curr Opin Genet Dev. 2008 Oct;18(5):455-60

Iyer J, Reich NC. Constitutive nuclear import of latent and activated STAT5a by its coiled coil domain. FASEB J. 2008 Feb;22(2):391-400

Koppikar P, Lui VW, Man D, Xi S, Chai RL, Nelson E, Tobey AB, Grandis JR. Constitutive activation of signal transducer and activator of transcription 5 contributes to tumor growth, epithelial-mesenchymal transition, and resistance to epidermal growth factor receptor targeting. Clin Cancer Res. 2008 Dec 1;14(23):7682-90

Bernaciak TM, Zareno J, Parsons JT, Silva CM. A novel role for signal transducer and activator of transcription 5b (STAT5b) in beta1-integrin-mediated human breast cancer cell migration. Breast Cancer Res. 2009;11(4):R52

Vogtenhuber C, Bucher C, Highfill SL, Koch LK, Goren E, Panoskaltsis-Mortari A, Taylor PA, Farrar MA, Blazar BR. Constitutively active Stat5b in CD4+ T cells inhibits graft-versus-host disease lethality associated with increased regulatory T-cell potency and decreased T effector cell responses. Blood. 2010 Jul 22;116(3):466-74

Du W, Wang YC, Hong J, Su WY, Lin YW, Lu R, Xiong H, Fang JY. STAT5 isoforms regulate colorectal cancer cell apoptosis via reduction of mitochondrial membrane potential and generation of reactive oxygen species. J Cell Physiol. 2011 Aug 8;

Koptyra M, Gupta S, Talati P, Nevalainen MT. Signal transducer and activator of transcription 5a/b: biomarker and therapeutic target in prostate and breast cancer. Int J Biochem Cell Biol. 2011 Oct;43(10):1417-21

Lopez TV, Lappin TR, Maxwell P, Shi Z, Lopez-Marure R, Aguilar C, Rocha-Zavaleta L. Autocrine/paracrine erythropoietin signalling promotes JAK/STAT-dependent proliferation of human cervical cancer cells. Int J Cancer. 2011 Dec 1;129(11):2566-76

Nadeau K, Hwa V, Rosenfeld RG. STAT5b deficiency: an unsuspected cause of growth failure, immunodeficiency, and severe pulmonary disease. J Pediatr. 2011 May;158(5):701-8

Peck AR, Witkiewicz AK, Liu C, Stringer GA, Klimowicz AC, Pequignot E, Freydin B, Tran TH, Yang N, Rosenberg AL, Hooke JA, Kovatich AJ, Nevalainen MT, Shriver CD, Hyslop T, Sauter G, Rimm DL, Magliocco AM, Rui H. Loss of nuclear localized and tyrosine phosphorylated Stat5 in breast cancer predicts poor clinical outcome and increased risk of antiestrogen therapy failure. J Clin Oncol. 2011 Jun 20;29(18):2448-58

*This article should be referenced as such:*

Del Rosario AM, Bernaciak TM, Silva CM. STAT5B (signal transducer and activator of transcription 5B). Atlas Genet Cytogenet Oncol Haematol. 2012; 16(2):106-110.