

## Gene Section

### Review

# E2F1 (E2F transcription factor 1)

Michael Zachariadis, Vassilios G Gorgoulis

University of Athens, Faculty of Medicine, Department of Anatomy, Greece (MZ), Department of Histology and Embryology, Molecular Carcinogenesis Group, Greece (VGG)

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### Identity

**Other names:** E2F-1; OTTHUMP00000030661; PBR3; RBAP-1; RBAP1; RBBP-3; RBBP3; RBP3

**HGNC (Hugo):** E2F1

**Location:** 20q11.22

**Local order:**

- C20orf114 31334.602 20q11.21 chromosome 20 open reading frame 114;
- CDK5RAP1 31410.306 20pter-q11.23 CDK5 regulatory subunit associated protein 1;
- CBFA2T2 31613.832 20q11 core-binding factor, runt domain, alpha subunit 2; translocated to, 2;
- E2F1 31727.150 20q11.2 E2F transcription factor 1;
- ASIP 32311.832 20q11.2-q12 agouti signaling protein, nonagouti homolog (mouse);
- ITCH 32414.745 20q11.22-q11.23 itchy homolog E3 ubiquitin protein ligase (mouse);
- DYNLRB1 32567.865 20q11.21 dynein, light chain, roadblock-type 1.

### DNA/RNA

**Note**

Start: 31,727,147 bp from pter.

End: 31,737,871 bp from pter.

Size: 10,725 bases.

Orientation: minus strand.

### Transcription

The gene is comprised of 7 exons, building one main transcript of 2506 bps.

### Pseudogene

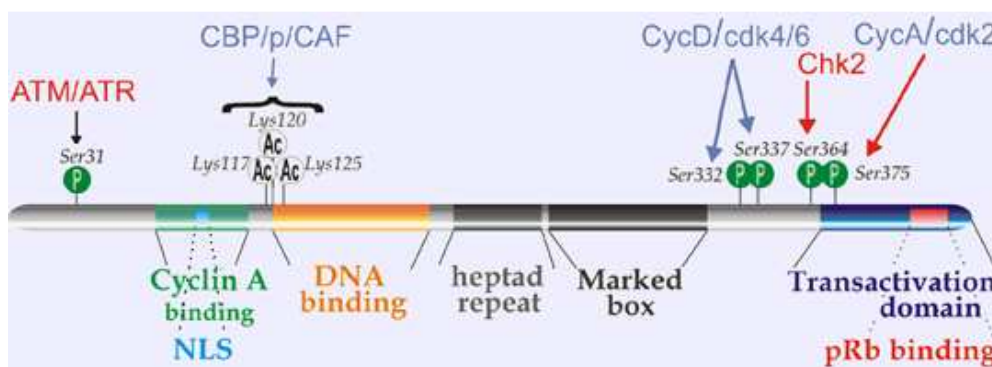
Non known pseudogenes.

### Protein

#### Description

Length: 437 aa, molecular weight: 46920 Da.

The protein contains a number of conserved domains, including a cyclin A binding domain (aa 67-108); a nuclear localization signal (NLS, aa 85-91); a helix-loop-helix DNA binding domain (aa 120-191); a heptad repeat (aa 201-243), which mediates homo/hetero dimerization; a marked box (245-317), which is implicated in the E2F/DP and E2F/E4 ORF 6/7 interaction, and is also essential for the apoptotic activity of E2F1; and a transactivation domain (aa 368-437) containing the pRB binding domain (aa 409-426). The E2F1 protein molecule is subject to a number of post-translational modifications, including phosphorylation by cyclin D/CDK4/CDK6 at serine residues 332 and 337, which stabilizes E2F1 and prevents its binding to pRB regardless of its phosphorylation status; acetylation of lysine residues 117, 120, and 125 by the factor acetyltransferase (FAT) complex CBP/p/CAF, which enhances DNA binding and stabilizes E2F1 further; phosphorylation by cyclin A/CDK2 at serine residue 375, which reduces DNA binding; and phosphorylation at serine residues 31 and 364 by ATM/ATR and CHK2 kinases, respectively, in response to DNA damage, which stabilizes E2F1 and promotes its apoptotic activity.



Schematic representation of human E2F1, depicting conserved domains and post-translational modification sites (see description for details).

### Expression

E2F1 is expressed in all actively proliferating tissues in a cell-cycle specific manner. It is expressed mainly at late G1 and G1/S transition, and its mRNA is absent or low during the rest of the cell cycle.

### Localisation

E2F1 is constitutively nuclear, due to a Nuclear Localization Signal (NLS) located around aa 90.

### Function

E2F1 represents a controversial player in cell cycle control, exhibiting a dual behavior, sometimes acting as a tumor-suppressor and others as an oncogene. E2F1 exerts transcriptional control over the cell cycle, induces apoptosis via distinct pathways, and participates in DNA damage response and checkpoint.

#### - Transcriptional control

E2F1 belongs to the E2F family of transcription factors, coordinating the expression of key genes involved in cell cycle regulation and progression. It is active during the G1 to S transition, and thus its target genes, which include regulatory elements of the cell cycle, such as CDC2, CDC25A and cyclin E, and essential components of DNA replication machinery, including DHFR, and DNA polymerase alpha, are expressed in a cell cycle dependent manner (i.e. only in late G1 and early S phase of the cell cycle). E2F1 recognizes and binds to specific DNA sequences (5'-TTTSSCGS-3', where S = C/G) that lie within the promoter of target genes, in the form of functional heterodimers with members of the DP family of transcription factors.

#### - Apoptosis

E2F1 can induce apoptosis via distinct P53-dependent and independent pathways.

The P53-independent pathways involve the p53 homolog P73 and APAF1, which are both transcriptionally controlled by E2F1. Transcriptional activation of P73 by E2F1 may lead to the activation of P53-responsive target genes, while induction of APAF1 transcription leads to activation of the caspase cascade.

Ultimately, both pathways lead to cell death by apoptosis. Moreover, E2F1 is implicated in the upregulation of the pro-apoptotic members of the BCL2 family, but also in the downregulation of anti-apoptotic signals, by inhibiting NF- $\kappa$ B activity, thereby enhancing also apoptosis.

There are many pathways linking E2F1 to P53-dependent apoptosis. The main mechanism involves direct transcriptional activation of the ARF tumor suppressor gene by E2F1. ARF sequesters MDM2 away from P53, leading consequently to P53 stabilization and activation. Nevertheless, ARF overexpression may lead to E2F1 downregulation, as ARF targets the latter for proteasomal degradation through skp2-dependent pathways. On the other hand, E2F1 can induce P53-dependent apoptosis in the absence of ARF. For instance, E2F1 can interact directly with P53 through the cyclin A-binding domain of E2F1, enhancing its apoptotic activity in response to DNA damage. Additionally, some reports argue that E2F1 uses the ATM pathway in order to activate both P53 and CHK2. Finally, E2F1 can augment the apoptotic capacity of P53 by enhancing the transcription of pro-apoptotic P53 cofactors such as P53-ASPP1, ASPP2, JMY and TP53INP1.

#### - DNA Damage Response

In response to DNA damage, E2F1 is upregulated through phosphorylation-mediated stabilization. E2F1 is phosphorylated at S31 by ATM/ATR kinases and at S364 by CHK2 kinase, which are all integral components of the DNA damage signaling pathway. These phosphorylations interfere with the ARF/SKP2- and MDM2-dependent degradation of E2F1, thus stabilizing the latter by decreasing its turnover rate. In response to IR or other agents that cause DNA double strand breaks, phosphorylation by ATM/ATR seems to prime E2F1 for acetylation at specific lysine residues. These acetylations are a prerequisite for the targeting of the P73 gene promoter by E2F1, which ultimately leads to apoptosis (see above paragraph). UV radiation does not trigger E2F1 acetylation and apoptosis. Instead, E2F1 seems to play a role in DNA repair and cell survival, either directly at the sites of DNA repair or

through modulation of DNA repair genes that are under its transcriptional control.

### Homology

Shares lesser or greater homology with other members of the E2F family (E2F2, E2F3, E2F4, E2F5, E2F6) and with the DP family of transcription factors (DP1, DP2).

## Mutations

### Note

No known mutations.

## Implicated in

### Note

Due to its pivotal and multifunctional role in cell cycle control, E2F1 is expected to be a significant player in carcinogenesis. Nevertheless, its paradoxical behavior, i.e. acting as an oncogene or a tumor suppressor depending on the cell context, renders its characterization and study challenging. Moreover, deregulation of E2F1 in cancer is often attributed to upstream alterations, in the pRB pathway that mainly regulates E2F function, and not to genetic mutations of its gene. The E2F1 paradox is quite evident in the various *in vitro* cellular systems and *in vivo* animal models that have been employed in order to study E2F1 function in cancer. Excess of E2F1 may promote proliferation, but at the same time it may also enhance apoptosis, and there are examples where overexpression or lack of E2F1 has both positive and negative effects on tumorigenesis. The delicate balance between growth and death seems to depend on the level of E2F1 deregulation, but also on the cell context background.

In non-small cell lung carcinomas (NSCLCs) E2F1 is significantly increased due to aberrant pRB status. In these cases the elevated levels of E2F1 are positively associated with the tumour growth index whereas apoptosis is not influenced as deregulation of the P53-MDM2 regulatory loop is a common phenomenon in NSCLC. Breast, thyroid and pancreatic cancer, seem to follow this same scenario, where aberrations in the pRB pathway coupled with defective P53 status, enhance E2F1 levels promoting tumor growth. In all these cases, the higher levels of E2F1 are also correlated with poorer outcome. Nevertheless, in other cases, like colon cancer, and diffuse large B-cell lymphomas the more aggressive disease is linked to lower E2F1 expression, as E2F1 in these cases acts as an oncosuppressor, enhancing apoptosis. Likewise, in adenocarcinomas of Barrett oesophagus E2F1 expression is negatively associated with tumor progression and positively with patient survival. In the case of transitional cell bladder carcinomas (TCCs) the findings are controversial. In one series of invasive bladder tumors E2F1 seems to play a tumor suppressive

role, while in another series of superficial low-grade TCCs E2F1 is positively correlated with proliferation, but not with apoptosis. This discrepancy seems to lie in the type of TCC examined and the molecular characteristics of the tissue.

The most usual genetic alteration of the E2F1 gene is amplification, as has been reported in several leukemic (e.g. the HEL human erythroleukemia cell line) and melanoma cell lines. The gene has also been found amplified in various esophageal, colorectal, cervical and ovarian cancers, as well as in lymph node metastases of melanoma, and is often linked to chromosome 20q gains in these entities. Importantly, in esophageal squamous cell carcinomas, the 20q gains and the amplification of the E2F1 gene are linked with greater aggressiveness and poorer prognosis.

## References

- Shan B, Zhu X, Chen PL, Durfee T, Yang Y, Sharp D, Lee WH. Molecular cloning of cellular genes encoding retinoblastoma-associated proteins: identification of a gene with properties of the transcription factor E2F. *Mol Cell Biol.* 1992 Dec;12(12):5620-31
- Chittenden T, Livingston DM, DeCaprio JA. Cell cycle analysis of E2F in primary human T cells reveals novel E2F complexes and biochemically distinct forms of free E2F. *Mol Cell Biol.* 1993 Jul;13(7):3975-83
- Flemington EK, Speck SH, Kaelin WG Jr. E2F-1-mediated transactivation is inhibited by complex formation with the retinoblastoma susceptibility gene product. *Proc Natl Acad Sci U S A.* 1993 Aug 1;90(15):6914-8
- Helin K, Harlow E, Fattaey A. Inhibition of E2F-1 transactivation by direct binding of the retinoblastoma protein. *Mol Cell Biol.* 1993 Oct;13(10):6501-8
- Krek W, Livingston DM, Shirodkar S. Binding to DNA and the retinoblastoma gene product promoted by complex formation of different E2F family members. *Science.* 1993 Dec 3;262(5139):1557-60
- Slansky JE, Li Y, Kaelin WG, Farnham PJ. A protein synthesis-dependent increase in E2F1 mRNA correlates with growth regulation of the dihydrofolate reductase promoter. *Mol Cell Biol.* 1993 Mar;13(3):1610-8
- La Thangue NB. DP and E2F proteins: components of a heterodimeric transcription factor implicated in cell cycle control. *Curr Opin Cell Biol.* 1994 Jun;6(3):443-50
- Lam EW, La Thangue NB. DP and E2F proteins: coordinating transcription with cell cycle progression. *Curr Opin Cell Biol.* 1994 Dec;6(6):859-66
- Neuman E, Flemington EK, Sellers WR, Kaelin WG Jr. Transcription of the E2F-1 gene is rendered cell cycle dependent by E2F DNA-binding sites within its promoter. *Mol Cell Biol.* 1994 Oct;14(10):6607-15
- O'Connor RJ, Hearing P. Mutually exclusive interaction of the adenovirus E4-6/7 protein and the retinoblastoma gene product with internal domains of E2F-1 and DP-1. *J Virol.* 1994 Nov;68(11):6848-62
- Adams PD, Kaelin WG Jr. Transcriptional control by E2F. *Semin Cancer Biol.* 1995 Apr;6(2):99-108
- Saito M, Helin K, Valentine MB, Griffith BB, Willman CL, Harlow E, Look AT. Amplification of the E2F1 transcription

- factor gene in the HEL erythroleukemia cell line. *Genomics*. 1995 Jan 1;25(1):130-8
- Adams PD, Sellers WR, Sharma SK, Wu AD, Nalin CM, Kaelin WG Jr. Identification of a cyclin-cdk2 recognition motif present in substrates and p21-like cyclin-dependent kinase inhibitors. *Mol Cell Biol*. 1996 Dec;16(12):6623-33
- Neuman E, Sellers WR, McNeil JA, Lawrence JB, Kaelin WG Jr. Structure and partial genomic sequence of the human E2F1 gene. *Gene*. 1996 Sep 16;173(2):163-9
- Campanero MR, Flemington EK. Regulation of E2F through ubiquitin-proteasome-dependent degradation: stabilization by the pRB tumor suppressor protein. *Proc Natl Acad Sci U S A*. 1997 Mar 18;94(6):2221-6
- Chen KY. Transcription factors and the down-regulation of G1/S boundary genes in human diploid fibroblasts during senescence. *Front Biosci*. 1997 Sep 1;2:d417-26
- Müller H, Moroni MC, Vigo E, Petersen BO, Bartek J, Helin K. Induction of S-phase entry by E2F transcription factors depends on their nuclear localization. *Mol Cell Biol*. 1997 Sep;17(9):5508-20
- Sladek TL. E2F transcription factor action, regulation and possible role in human cancer. *Cell Prolif*. 1997 Mar-Apr;30(3-4):97-105
- Helin K. Regulation of cell proliferation by the E2F transcription factors. *Curr Opin Genet Dev*. 1998 Feb;8(1):28-35
- Inoshita S, Terada Y, Nakashima O, Kuwahara M, Sasaki S, Marumo F. Regulation of the G1/S transition phase in mesangial cells by E2F1. *Kidney Int*. 1999 Oct;56(4):1238-41
- Marti A, Wirbelauer C, Scheffner M, Krek W. Interaction between ubiquitin-protein ligase SCFSKP2 and E2F-1 underlies the regulation of E2F-1 degradation. *Nat Cell Biol*. 1999 May;1(1):14-9
- Yamasaki L. Balancing proliferation and apoptosis in vivo: the Goldilocks theory of E2F/DP action. *Biochim Biophys Acta*. 1999 Mar 25;1423(2):M9-15
- Zheng N, Fraenkel E, Pabo CO, Pavletich NP. Structural basis of DNA recognition by the heterodimeric cell cycle transcription factor E2F-DP. *Genes Dev*. 1999 Mar 15;13(6):666-74
- Martelli F, Hamilton T, Silver DP, Sharpless NE, Bardeesy N, Rokas M, DePinho RA, Livingston DM, Grossman SR. p19ARF targets certain E2F species for degradation. *Proc Natl Acad Sci U S A*. 2001 Apr 10;98(8):4455-60
- Ohta T, Xiong Y. Phosphorylation- and Skp1-independent in vitro ubiquitination of E2F1 by multiple ROC-cullin ligases. *Cancer Res*. 2001 Feb 15;61(4):1347-53
- Phillips AC, Vousden KH. E2F-1 induced apoptosis. *Apoptosis*. 2001 Jun;6(3):173-82
- Ginsberg D. E2F1 pathways to apoptosis. *FEBS Lett*. 2002 Oct 2;529(1):122-5
- Gorgoulis VG, Zacharatos P, Mariatos G, Kotsinas A, Bouda M, Kletsas D, Asimacopoulos PJ, Agnantis N, Kittas C, Papavassiliou AG. Transcription factor E2F-1 acts as a growth-promoting factor and is associated with adverse prognosis in non-small cell lung carcinomas. *J Pathol*. 2002 Oct;198(2):142-56
- Kotsinas A, Evangelou K, Zacharatos P, Kittas C, Gorgoulis VG. Proliferation, but not apoptosis, is associated with distinct beta-catenin expression patterns in non-small-cell lung carcinomas: relationship with adenomatous polyposis coli and G(1)-to S-phase cell-cycle regulators. *Am J Pathol*. 2002 Nov;161(5):1619-34
- Lee C, Chang JH, Lee HS, Cho Y. Structural basis for the recognition of the E2F transactivation domain by the retinoblastoma tumor suppressor. *Genes Dev*. 2002 Dec 15;16(24):3199-212
- Trimarchi JM, Lees JA. Sibling rivalry in the E2F family. *Nat Rev Mol Cell Biol*. 2002 Jan;3(1):11-20
- Cam H, Dynlacht BD. Emerging roles for E2F: beyond the G1/S transition and DNA replication. *Cancer Cell*. 2003 Apr;3(4):311-6
- Fujita Y, Sakakura C, Shimomura K, Nakanishi M, Yasuoka R, Aragane H, Hagiwara A, Abe T, Inazawa J, Yamagishi H. Chromosome arm 20q gains and other genomic alterations in esophageal squamous cell carcinoma, as analyzed by comparative genomic hybridization and fluorescence in situ hybridization. *Hepatogastroenterology*. 2003 Nov-Dec;50(54):1857-63
- Hallstrom TC, Nevins JR. Specificity in the activation and control of transcription factor E2F-dependent apoptosis. *Proc Natl Acad Sci U S A*. 2003 Sep 16;100(19):10848-53
- Mundle SD, Saberwal G. Evolving intricacies and implications of E2F1 regulation. *FASEB J*. 2003 Apr;17(6):569-74
- Stevens C, La Thangue NB. A new role for E2F-1 in checkpoint control. *Cell Cycle*. 2003 Sep-Oct;2(5):435-7
- Xiao B, Spencer J, Clements A, Ali-Khan N, Mittnacht S, Broceño C, Burghammer M, Perrakis A, Marmorstein R, Gamblin SJ. Crystal structure of the retinoblastoma tumor suppressor protein bound to E2F and the molecular basis of its regulation. *Proc Natl Acad Sci U S A*. 2003 Mar 4;100(5):2363-8
- Attwooll C, Lazzarini Denchi E, Helin K. The E2F family: specific functions and overlapping interests. *EMBO J*. 2004 Dec 8;23(24):4709-16
- Bell LA, Ryan KM. Life and death decisions by E2F-1. *Cell Death Differ*. 2004 Feb;11(2):137-42
- Crosby ME, Almasan A. Opposing roles of E2Fs in cell proliferation and death. *Cancer Biol Ther*. 2004 Dec;3(12):1208-11
- Karakaidos P, Taraviras S, Vassiliou LV, Zacharatos P, Kastrinakis NG, Kougiou D, Kouloukoussa M, Nishitani H, Papavassiliou AG, Lygerou Z, Gorgoulis VG. Overexpression of the replication licensing regulators hCdt1 and hCdc6 characterizes a subset of non-small-cell lung carcinomas: synergistic effect with mutant p53 on tumor growth and chromosomal instability--evidence of E2F-1 transcriptional control over hCdt1. *Am J Pathol*. 2004 Oct;165(4):1351-65
- Knezevic D, Brash DE. Role of E2F1 in apoptosis: a case study in feedback loops. *Cell Cycle*. 2004 Jun;3(6):729-32
- Pardee AB, Li CJ, Reddy GP. Regulation in S phase by E2F. *Cell Cycle*. 2004 Sep;3(9):1091-4
- Rogoff HA, Kowalik TF. Life, death and E2F: linking proliferation control and DNA damage signaling via E2F1. *Cell Cycle*. 2004 Jul;3(7):845-6
- Stevens C, La Thangue NB. The emerging role of E2F-1 in the DNA damage response and checkpoint control. *DNA Repair (Amst)*. 2004 Aug-Sep;3(8-9):1071-9
- Zacharatos P, Kotsinas A, Evangelou K, Karakaidos P, Vassiliou LV, Rezaei N, Kyroudi A, Kittas C, Patsouris E, Papavassiliou AG, Gorgoulis VG. Distinct expression patterns of the transcription factor E2F-1 in relation to tumour growth parameters in common human carcinomas. *J Pathol*. 2004 Jul;203(3):744-53

- Rubin SM, Gall AL, Zheng N, Pavletich NP. Structure of the Rb C-terminal domain bound to E2F1-DP1: a mechanism for phosphorylation-induced E2F release. *Cell*. 2005 Dec 16;123(6):1093-106
- DeGregori J, Johnson DG. Distinct and Overlapping Roles for E2F Family Members in Transcription, Proliferation and Apoptosis. *Curr Mol Med*. 2006 Nov;6(7):739-48
- Johnson DG, Degregori J. Putting the Oncogenic and Tumor Suppressive Activities of E2F into Context. *Curr Mol Med*. 2006 Nov;6(7):731-8
- Koutsami MK, Tsantoulis PK, Kouloukoussa M, Apostolopoulou K, Pateras IS, Spartinou Z, Drougou A, Evangelou K, Kittas C, Bartkova J, Bartek J, Gorgoulis VG. Centrosome abnormalities are frequently observed in non-small-cell lung cancer and are associated with aneuploidy and cyclin E overexpression. *J Pathol*. 2006 Aug;209(4):512-21
- Apostolopoulou K, Pateras IS, Evangelou K, Tsantoulis PK, Lontos M, Kittas C, Tiniakos DG, Kotsinas A, Cordon-Cardo C, Gorgoulis VG. Gene amplification is a relatively frequent event leading to ZBTB7A (Pokemon) overexpression in non-small cell lung cancer. *J Pathol*. 2007 Nov;213(3):294-302
- Pützer BM. E2F1 death pathways as targets for cancer therapy. *J Cell Mol Med*. 2007 Mar-Apr;11(2):239-51
- van Deursen JM. Rb loss causes cancer by driving mitosis mad. *Cancer Cell*. 2007 Jan;11(1):1-3
- Verdaguer E, Susana Gde A, Clemens A, Pallàs M, Camins A. Implication of the transcription factor E2F-1 in the modulation of neuronal apoptosis. *Biomed Pharmacother*. 2007 Aug;61(7):390-9
- Wang L, Wang R, Herrup K. E2F1 works as a cell cycle suppressor in mature neurons. *J Neurosci*. 2007 Nov 14;27(46):12555-64
- Alonso MM, Alemany R, Fueyo J, Gomez-Manzano C. E2F1 in gliomas: a paradigm of oncogene addiction. *Cancer Lett*. 2008 May 18;263(2):157-63
- Evangelou K, Kotsinas A, Mariolis-Sapsakos T, Giannopoulos A, Tsantoulis PK, Constantinides C, Troupis TG, Salmas M, Kyroudis A, Kittas C, Gorgoulis VG. E2F-1 overexpression correlates with decreased proliferation and better prognosis in adenocarcinomas of Barrett oesophagus. *J Clin Pathol*. 2008 May;61(5):601-5
- Gao XN, Yu L. E2F1 contributes to the transcriptional activation of the KIR3DL1 gene. *Biochem Biophys Res Commun*. 2008 Jun 6;370(3):399-403
- Hu XT. TGFbeta-mediated formation of pRb-E2F complexes in human myeloid leukemia cells. *Biochem Biophys Res Commun*. 2008 May 2;369(2):277-80
- Jun DY, Park HS, Lee JY, Kim YH. Regulation of the human mitotic centromere-associated kinesin (MCAK) promoter by the transcription factors Sp1 and E2F1. *Biochim Biophys Acta*. 2008 May;1779(5):356-61
- Kim K, Oh M, Ki H, Wang T, Bareiss S, Fini ME, Li D, Lu Q. Identification of E2F1 as a positive transcriptional regulator for delta-catenin. *Biochem Biophys Res Commun*. 2008 May 2;369(2):414-20
- Marlowe JL, Fan Y, Chang X, Peng L, Knudsen ES, Xia Y, Puga A. The aryl hydrocarbon receptor binds to E2F1 and inhibits E2F1-induced apoptosis. *Mol Biol Cell*. 2008 Aug;19(8):3263-71
- Scotto L, Narayan G, Nandula SV, Arias-Pulido H, Subramaniam S, Schneider A, Kaufmann AM, Wright JD, Pothuri B, Mansukhani M, Murty VV. Identification of copy number gain and overexpressed genes on chromosome arm 20q by an integrative genomic approach in cervical cancer: potential role in progression. *Genes Chromosomes Cancer*. 2008 Sep;47(9):755-65

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*This article should be referenced as such:*

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