Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Review

E2F3 (E2F transcription factor 3)

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Identity

Other names: E2F-3; KIAA0075; Y10479

HGNC (Hugo): E2F3

Location: 6p22.3

Local order: tel-OACT1-E2F3-CDKAL1-cen.

DNA/RNA

Description

The gene has 7 exons (two alternative exons 1) and 6 introns comprising 91545 bp.

Transcription

Transcription takes place in a centromeric -> telomeric orientation. The length of the processed mRNA is about 4744 bp. EMBL lists two alternativly spliced forms other than those concerning exons 1a/b.

Pseudogene

2q33-q35, 17q11-q12.

Protein

Description

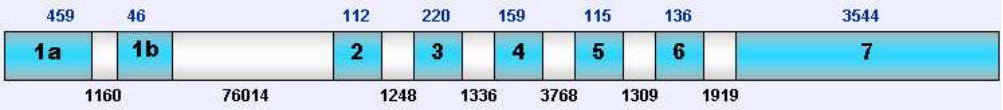
E2F3A comprises 465 amino acid residues (49 kDa), E2F3B comprises 334 amino acid residues.

Expression

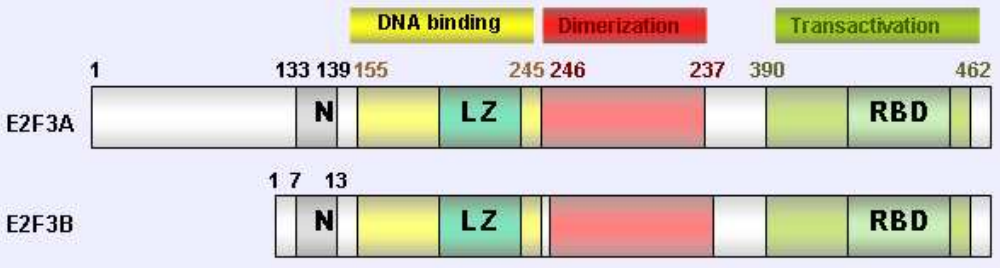
Ubiquitous.

Localisation

Nuclear.



Schematic diagram of the E2F3 gene comprising 7 exons (in blue). Exons 1a or 1b are used alternatively to produce variants E2F3A or E2F3B, respectively. The sizes in base pairs (bp) of exons (above) and introns (below) are shown.



Schematic diagram of E2F3 protein structure. E2F3A is shown in the upper part, E2F3B below. The proteins differ in their N-terminal regions comprising 132 and 6 amino acid residues, respectively. N: nuclear localization sequence, LZ: leucine zipper (blue), RBD: pRB binding domain (light blue). DNA binding domain (yellow), dimerization domain (red), transactivation domain (green). The positions of amino acid residues are indicated.

Function

E2F3 is a sequence-specific transcription factor implicated in cell cycle regulation (S-phase). It is a transcriptional activator for E2F-responsive genes. E2F proteins heterodimerize with DP proteins and are subject to inhibition by binding to the pocket domain of retinoblastoma protein (pRB). Phosphorylation of pRB sets E2F proteins free to regulate their target genes.

Homology

E2F transcription factor family consists of E2F-proteins (E2F1-6) and DP-proteins (DP1, DP2).

Mutations

Note

Gene mutations have not been described hitherto.

Germinal

Not known.

Somatic

Not known.

Implicated in

amp(6)(p22)

Note

Medium-to-high-level genomic amplification sometimes resulting in HSR formation and believed to target E2F3 which lies within the common amplified region (see image below). Genomic amplification may not be required for over-expression.

Disease

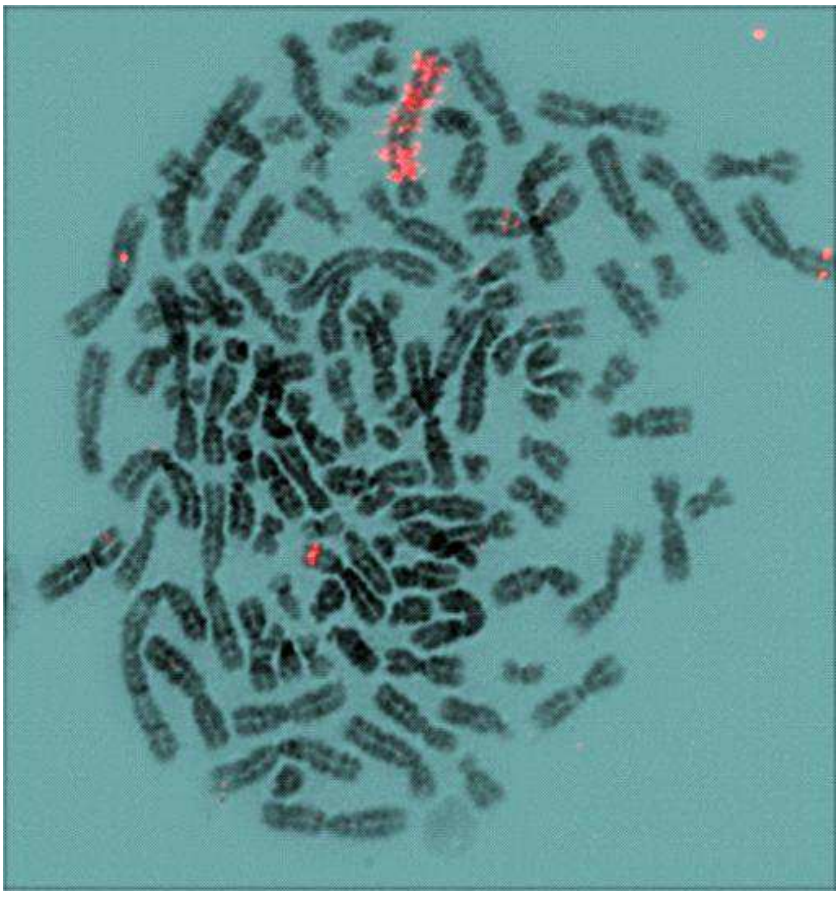
Notably, bladder and prostate cancers.

Prognosis

Associated with invasiveness in bladder cancer, and with poor survival in prostate cancer. Circa 33% of primary transitional cell carcinomas of the bladder overexpress nuclear E2F3 protein.

Cytogenetics

Presumptive target of genomic amplification at 6p22 in bladder cancer where it effects E2F3 overexpression (as exemplified by the bladder cancer cell lines 5637 and HT-1367).



Genomic amplification of E2F3: FISH image shows HT-1376 bladder cancer cell line (DSMZ acc 397) hybridized with a BAC clone (RPMI-99F1) covering the E2F3 locus at 6p22.3. (See breakpoint diagram below for map.) Note high level genomic amplification comprising multiple tandemly repeated copies of E2F3 via formation of an homogeneously staining region (HSR) in a marker chromosome - a hallmark of oncogene activity. Similar findings have been reported in both primary bladder and prostate cancers. Analysis of E2F3 protein has confirmed overexpression in cell lines evidencing genomic amplification, including HT-1376 as well as 5637 (DSMZ acc 35) and TCC-SUP (DSMZ acc 377).

However, E2F3 may not be the only target gene inside the common amplified region.

Hybrid/Mutated gene
Not yet reported.

t(6;9)(p22;p13)

Note
Observed in a DLBCL cell line: yet to be described clinically.

Disease
Diffuse large B-cell lymphoma (DLBCL).

Prognosis
Unknown.

Cytogenetics
Breakpoint lies upstream of E2F3 and juxtaposes upstream (regulatory) region of PAX5.

Hybrid/Mutated gene
Not yet reported.

Oncogenesis
E2F3 behaves like a classical oncogene and is subject to upregulation via genomic amplification in bladder and prostate cancers.

Upregulated E2F3 stimulates cycle progression and proliferation. E2F3 transcription is induced by MYC and these together conspire to promote G1/S-phase transition.
This activity is negatively regulated by binding of the E2F transactivation domain to RB1 or p107. In prostate cancer, oncogenesis directed by E2F3 may be mediated by the polycomb group protein Enhancer of Zeste Homolog gene 2 (EZH2). E2F3 may also activate survivin transcription. In Hodgkin lymphoma which, though lacking recurrent chromosomal rearrangements at 6p22, shows a pattern of gene dysregulation reminiscent of prostate cancer, E2F3 regulates HLXB9 expression which in turn drives IL-6 expression thought to play a central role in this enigmatic tumor. E2F3 may also act as a tumor suppressor though the supporting evidence is tentative. Thus, while E2F3 loss results in centrosome defects associated with aneuploidy and promote metastasis of medullary thyroid carcinoma, E2F3 -/- mice show no excess tumor incidence. Furthermore, loss of E2F3 has been associated with suppression of pituitary tumors.

Breakpoints

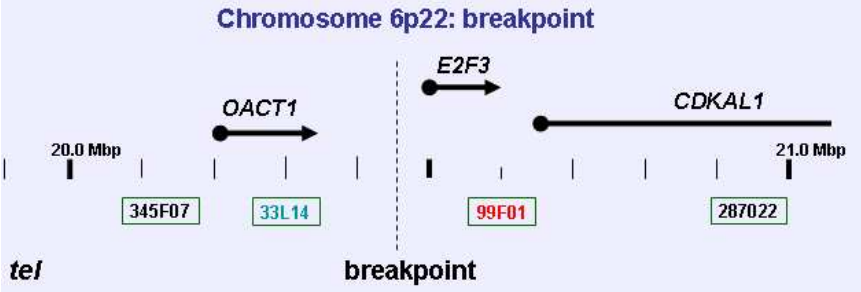


Figure depicts location of sole E2F3 breakpoint described hitherto, lying approximately 50-150 Kbp upstream of the transcription unit as detected in a complex t(6;9)(p22;p13) in a DLBCL cell line. The upstream region of E2F3 is thus juxtaposed with the upstream regulatory region of PAX5. Figure shows genes flanking E2F3 together with RPCI-11 library clones.

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