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Gene Section
Review

FOXP1 (forkhead box P1)

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Identity

Hugo: FOXP1
Other names: 12CC4; FLJ23741; hFKH1B; HSPC215; MGC12942; MGC88572; MGC9551; QRF1 (Glutamine-Rich Factor 1)
Location: 3p14.1
Local order: 3p telomere-3' FOXP1 5'-centromere.
Note: chr3: 71087426-71715830 bps.

DNA/RNA

Description

21 exons; the first 5 exons, the 5' part of exon 6 and the 3' part of exon 21 are non-coding.

Transcription

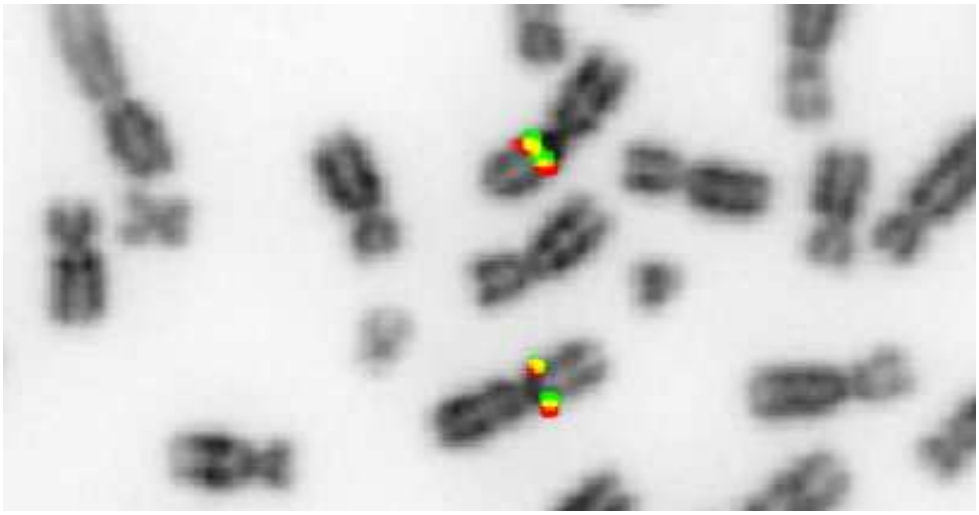
628405 bps mRNA; transcribed in a centromeric to telomeric orientation. Alternative splicing; 4 named isoforms (Q9H334-1,-2,-3,-4) recognized.

Protein

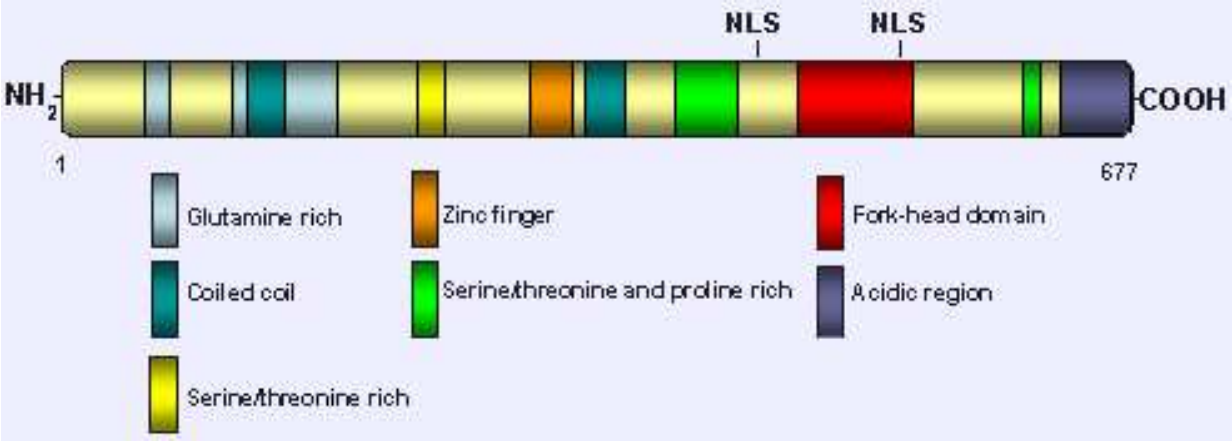
Note: Forkhead box P1

Description

The FOXP1 protein is 677-amino acid long and its molecular weight is 75317 Da. It contains two potential nucleic acid-binding motifs, including a forkhead (winged-helix) domain and C2H2 zinc finger domain. Other regions that may regulate transcription and mediate protein-protein interaction include coiled-coil, glutamine rich, S/T-rich, S/T/P-rich and acidic rich domains. Two potential nuclear localization signals (NLS) were identified at amino acid 434-440 and amino acid 543-546. Two potential PEST motifs are predicted in the acidic region near its COOH terminus. The FOXP1 protein contains a number potential of cyclin-cdk phosphorylation sites and a recognition site for the p70S6-kinase which is itself regulated by the PI(3)K. The FOXP1 protein forms homodimers and heterodimers with FOXP2 and FOXP4. Dimerization is required for DNA-binding.



(3p14.1): RP11-154H23 (Spectrum0range) and RP11-79P21 (SpectrumGreen) covering the 5' and the 3'end of FOXP1, respectively.



Schematic diagram of the Foxp1 protein indicating the localization of predicted domains and motifs. Modified from Banham AH et al., Cancer Res 61, 8820-8820, 2001.

Expression

Ubiquitous expression in normal adult and fetal human tissues; highest expression in lymphoid and gastrointestinal tissues. Within the B lineage, FOXP1 is expressed modestly in progenitors, with highest levels in activated B cells and mantle zone B cells.

Localisation

Predominantly nuclear

Function

FOXP1 can act as a transcriptional repressor. The gene has a broad range of functions and plays an important role in cardiac and lung development, B-cell development and macrophage differentiation. FOXP1 is implicated in malignancy.

Homology

Member of the broadly expressed FOXP subfamily which itself is a part of the FOX gene family of transcription factors, characterized by sharing a common DNA binding domain termed forkhead or a winged-helix domain. FOXP proteins (FOXP1, -2, -3, -4) play important roles in immune responses, organ development and cancer pathogenesis.

Implicated in

t(3;9)(p14;p13) ⟶ PAX5-FOXP1 in childhood ALL

Disease

B-progenitor ALL (single case).

Cytogenetics

Unknown.

Abnormal Protein

Contains the NH2 terminus of PAX5 with the DNA-binding paired, octapeptide and homeodomain-like domains and the COOH-terminus of FOXP1 containing its DNA-binding (Zn and FH) and transcriptional regulatory domains.

Oncogenesis

The fusion protein is predicted to retain the ability to bind to PAX5 and FOXP1 transcriptional targets, but no longer provide normal transcriptional regulatory functions of both genes.

t(3;14)(p14;q32) /B-cell malignancies IGH -FOXP1

Disease

t(3;14)(p14;q32) resulting in upregulated expression of FOXP1, is a rare aberration in B-NHL. The translocation occurs recurrently in MALT-type of marginal zone B-cell lymphomas (MZBCL) and diffuse large B cell lymphoma (DLBCL). Single cases with variant FOXP1 translocations involving unknown non-IG loci have been reported.
Of note, a significant number of DLBCL (with a predominantly ABC-like phenotype) and extranodal MZBCL displayed a strong expression of FOXP1 which is independent of genomic rearrangements of the FOXP1 locus. FOXP1-positivity was also found in numerous cases of cutaneous B-cell lymphomas and follicular lymphomas.

Prognosis

High expression of FOXP1 in DLBCL is associated with poor prognosis. Deregulation of FOXP1 in MALT lymphomas possibly leads to transformation to a more aggressive DLBCL.

Cytogenetics

t(3;14) was recorded as a sole aberration and as a part of complex karyotypes. In MALT lymphomas, translocations involving FOXP1, MALT1 and BCL10 are mutually exclusive.

Hybrid/Mutated Gene

No hybrid gene; 5' FOXP1 juxtaposed with 3' IGH enhancer. Molecular characteristics of FOXP1 variant translocations are unknown.

Oncogenesis

The occurrence of activated FOXP1 translocations in lymphoma indicates that FOXP1 functions as an oncogene. So far, mechanisms and molecular consequences of aberrant expression of FOXP1 in lymphomas not harboring 3p14/FOXP1 rearrangements are unknown. The preliminary data suggest that not the full-length protein, but smaller FOXP1 isoforms are atypically highly expressed in ABC-DLBCL cell lines. Their role in the disease process is currently investigated.

Solid tumors

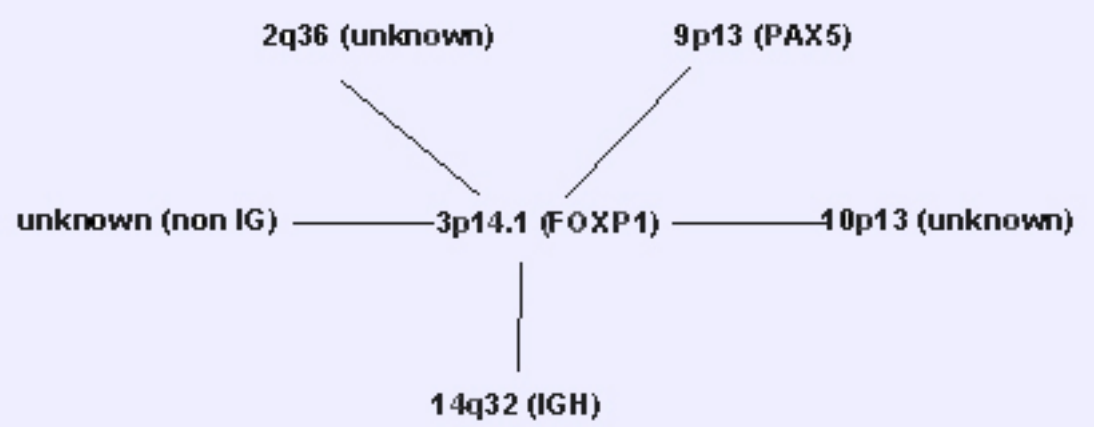
Disease

FOXP1 abnormalities (overexpression, mislocalization or loss of FOXP1) are observed in a wide variety of cancers, particularly of epithelial origin.

FOXP1 located in the 3p region frequently deleted in multiple types of cancers is one of a few potential tumor suppressor genes. Genomic loss of FOXP1 correlates with a decrease in FOXP1 mRNA and/or a decrease in FOXP1 protein levels in a significant number of analyzed lung cancers and head and neck cancers. In addition, an aberrant cytoplasmic localization of FOXP1 has been observed in a number of epithelial malignancies. Whether that aberrant localization may be a mechanism for inactivation of FOXP1 remains to be determined. So far, the direct evidence that FOXP1 functions as a tumor suppressor gene is limited.

In contrast, increased nuclear expression of FOXP1 has been detected in renal cell carcinoma, some prostate cancers, endometrial cancers and breast cancers. The mechanisms leading to altered expression of FOXP1 in cancer are elusive.

Breakpoints



Recurrent (14q32/IGH) and non-recurrent chromosomal breakpoints/partners involved in the FOXP1 rearrangements in hematological malignancies.

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