

Gene Section

Review

TP53 (tumor protein p53 (Li-Fraumeni syndrome))

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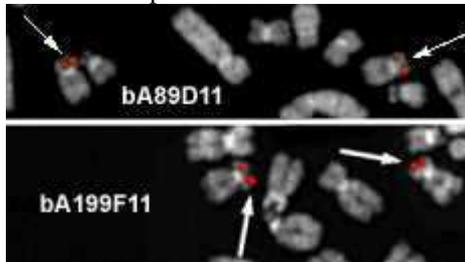
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Identity

Hugo: TP53

Other names: P53 (Protein 53 kDa)

Location: 17p13



Probe(s) - Courtesy Mariano Rocchi.

DNA/RNA

Description

The gene encompasses 20 kb of DNA; 11 exons (the first is non-coding).

Transcription

3.0 kb mRNA; 1179 bp open reading frame.

Protein

Description

393 amino acids; 53 kDa protein; numerous post translational modifications: phosphorylation, acetylation, ubiquitination, sumoylation, neddylation. Contains from N-term to C-term, a transactivation domain (1-42), a Proline rich domain (63-97), a specific DNA binding domain (102-292), 3 nuclear

localization signals (305-322), a tetramerization domain that include a nuclear export signal (325-355) and a negative regulatory domain (360-393).

Expression

Widely expressed.

Localisation

Nucleus.

Function

Tumour suppressor gene. P53 is a transcription factor present at minute level in any normal cells. Upon various types of stress (DNA damage, hypoxia, nucleotide pool depletion, viral infection, oncogene activation), posttranslational modification lead to p53 stabilisation and activation. Although the number of genes activated by p53 is rather large, the outcome of p53 activation is either cell cycle arrest in G1 (by p21), in G2 (by 14-3-3 s) or apoptosis (by BAX, PUMA or NOXA). The cell growth arrest activity of p53 allows the activation of the DNA repair system of the cell.

Homology

The five domains are highly-conserved regions between species (from human to fly). Two new genes homologous to p53 have been discovered, p73 localized at 1p36 and p63 localized at 3q27.

Mutations

Germinal

In Li-Fraumeni syndrome, a dominantly inherited disease in which affected individuals are predisposed to develop sarcomas, osteosarcomas, leukemias and breast

cancers at unusually early ages. Inherited TP53 mutations are associated with Li-Fraumeni and Li-Fraumeni-like syndromes, characterized by a familial clustering of tumors, with a predominance of soft tissue and bone sarcomas, breast cancers, brain tumors, and adrenocortical carcinomas, diagnosed before the age of 45 years.

Somatic

P53 is mutated in about 50% of human cancers, and the non-mutated allele is generally lost. The frequency and the type of mutation may vary from one tumour type to another. Somatic TP53 mutations are frequent in most human cancers, ranging from 5% to 80% depending on the type, stage and etiology of tumors. Most mutations are missense (75%) and other include non-sense (7.5%), deletions, insertions or splicing mutations (17.5%). There are some hot-spots for mutations at CpG dinucleotides at codon positions 175, 248, 273 and 282. TP53 gene mutation is a marker of bad prognosis in a number of cancers, such as breast cancer. Specific mutation spectra are observed in lung, liver and skin cancer that are related to specific carcinogen exposure (tobacco smoke, aflatoxin and UV respectively).

Implicated in

Li-Fraumeni syndrome (LFS)

Disease

Autosomal dominant condition, cancer prone disease, Li-Fraumeni syndrome (LFS) is defined by the existence of a proband with early onset sarcoma and a first degree relative with cancer before 45 years, plus another first/second degree relative with cancer at before 45 years or sarcoma at any age. Clinical definitions for Li-Fraumeni like syndromes (LFL) have also been proposed by Eeles and Birch. Germline mutation of TP53 is found in about 70% of LFS and 50% of LFL cases. In a few cases of LFS/LFL families free of TP53 mutations, germline mutations in genes connected to the p53 pathway have been found: CHK2, PTEN, CDKN2A.

Prognosis

Most common cancer in Li-Fraumeni children (before the age of 10 years) are: soft tissues sarcoma, brain tumors and adrenocortical carcinomas; osteosarcoma predominate in adolescents; afterwards, female breast cancer, soft tissue sarcomas and brain tumors prevail, and other less frequent cancers such as leukaemias or colon carcinomas are also observed. Multiple primary cancers are quite characteristic of Li-Fraumeni syndrome but may also be representative of Bloom's syndrome. Cancers in this disease, as in other cancer-prone diseases, often occur early in life: 50% of patients aged 30 years have had a cancer (i.e.

penetrance is 50%, according to this disease definition), and penetrance is 90% at age 60 years.

Oncogenesis

(Known) germinal mutations are variable, but are mostly missense mutations located in exons 4 to 10. In tumours occurring in these patients, the other (wild-type) allele is often lost, in accordance with the two-hit model for neoplasia.

Haematological malignancies

Oncogenesis

TP53 gene alterations have been found in:

- 20-30% of blast crisis CML (mostly in the myeloid type), often associated with i(17q).
 - 5% of MDS cases and 15% of ANLL often with a visible del(17p).
 - 2% of ALL (but with high variations according to the ALL type, reaching 50% of L3 ALL and Burkitt lymphomas).
 - 15% of CLL (and 40% in the aggressive CLL transformation into the Richter's syndrome) and 30% of adult T-cell leukaemia (only found in the aggressive form).
 - 5-10% of multiple myelomas.
 - 60-80% of Hodgkin disease.
 - 30% of high grade B-cell NHL (rare in low grade NHL), and 50% of HIV-related NHL.
- TP53 gene alterations in haematological malignancies are associated with a poor prognosis.

Skin cancers

Disease

Skin cancers include basal cell carcinomas, squamous cell carcinomas, and melanomas.

Prognosis

Highly different according to the pathological group.

Oncogenesis

TP53 is mutated in 40% of basal cell carcinomas and squamous cell carcinomas while mutations are infrequent in malignant melanoma. The pattern of TP53 mutation in skin cancer is highly related to UV exposure with a high frequency of CC→TT and C→T transitions and specific hotspots at codons 196 and 278.

Melanoma

Disease

Melanoma is a malignant tumor of melanocytes. Epidemiologic evidence suggests that exposure to ultraviolet (UV) radiation and the sensitivity of an individual's skin to UV radiation are risk factors for skin cancer including melanoma.

Oncogenesis

TP53 gene mutations are rare in melanoma. They often lose Apaf-1, a cell-death effector that acts with cytochrome c and caspase-9 to mediate p53-dependent

apoptosis. It may contribute to the low frequency of TP53 mutations observed in this highly chemoresistant tumour type.

Breast cancer

Oncogenesis

TP53 is mutated in 25% of breast cancers with hotspots at codons 175, 220, 245, 248, 273. Geographical variations in mutation patterns have been observed. The prevalence of mutations is higher in large size, high grade and estrogen receptor negative tumors. It is also higher in BRCA1-related tumors. TP53 mutation is a factor of poor prognosis independently of tumor stage and hormone receptor content. It is associated with poor response to doxorubicin therapy.

Head and neck squamous cell carcinoma

Disease

Head and neck cancer is an important health problem around the world accounting for approximately 500000 new cases each year. The carcinogenesis of head and neck results from a dysregulation of cellular proliferation, differentiation and cell death. The major etiologic agents are tobacco and alcohol consumption and for some cases human papilloma virus (HPV) infection.

Oncogenesis

TP53 mutation can be found in about 40-60% of HNSCC cancers and is thought to be an early event as it is often detected in precancerous lesions. TP53 mutation is associated with poor prognosis in HNSCC.

Lung cancers

Disease

Lung cancers are neuroendocrine lung tumours (small cell lung carcinomas, carcinoids, large cell neuroendocrine carcinomas) or non neuroendocrine lung tumours (squamous carcinomas, adenocarcinomas, large cell carcinomas).

Oncogenesis

Is multistep, through C-MYC or N-MYC activation, H-RAS1 or K-RAS2 mutation, P53, RB1, and P16 inactivation, loss of heterozygosity (LOH) at 3p, 13q, 17p. TP53 is mutated in 40% of lung cancers with frequent G→T transversions at codons 157, 158, 245, 248, 249 and 273. These mutations are linked to exposure to tobacco smoke. TP53 gene mutations may be associated with bad prognosis.

Oesophagus cancers

Disease

Two main forms: squamous cell carcinoma and adenocarcinoma.

Oncogenesis

TP53 is mutated in 45% of oesophageal cancers with hotspots at codons 175, 176, 248, 273, 282. It is thought to be an early event as it is often detected in precancerous lesions.

Liver cancer

Cytogenetics

Losses of 1p, 4q, 5p, 5q, 8q, 13q, 16p, 16q, and 17p in 20 to 50% of cases.

Oncogenesis

Specific mutation at codon 249 related to aflatoxin B1 dietary exposure in exposed area (China, Africa); low frequency of mutation in developed countries.

Gastric cancer

Disease

Risk factors for gastric cancer include: Helicobacter pylori gastric infection, advanced age, male gender, diet including dry salted foods, atrophic gastritis, pernicious anemia, cigarette smoking, Menetrier's disease, and familial polyposis. Adenocarcinoma histology accounts for 90% to 95% of all gastric malignancies. The prognosis of patients with gastric cancer is related to tumor extent and includes both nodal involvement and direct tumor extension beyond the gastric wall. Tumor grade may also provide some prognostic information.

Oncogenesis

TP53 mutations are found in about 30% of gastric cancer with a spectrum similar to the one of colorectal cancer. The prognostic value of these mutations is unknown.

Colorectal cancers

Disease

There are two types of colorectal cancers, according to the ploidy:

-The diploid form, RER+ (Replication Error+), sporadic, without loss of heterozygosity (LOH), with few mutations of p53 and APC, and right-sided.

-The polyploid form, RER-, with LOH (5q, 17p, 18q), mutations in p53, and more often left-sided, they have a worse prognosis.

Prognosis

Survival, although improving, is not much more than 50% after 5 years.

Cytogenetics

Diploid tumours without frequent allelic losses; aneuploid tumours with numerous allelic losses; LOH on chromosomes 17 and 18 in more than 75% of cases; other chromosome arms losses in about 50% of cases.

Oncogenesis

A number of genes are known to be implicated in tumour progression in colorectal cancers: APC, P53, KRAS2, mismatch repair genes (MMR genes). TP53 is mutated in 45% of colorectal cancer cases with a majority of C→T transitions at CpG sites and hotspots at codons 175, 245, 248, 273 and 282. TP53 mutation may be associated with poor prognosis in patient treated with chemotherapy.

Bladder cancer**Prognosis**

Highly variable, according to the stage and the grade.

Cytogenetics

-9, -11 or del(11p), del(17p) and LOH at 17p, del(13q), frequent other LOH, aneuploidy, polyploidy, complex karyotypes.

Oncogenesis

Multi-step and largely unknown process; loss of 9q and P53 mutations would be early events; RB1, and P16 inactivation, EGFR overexpression, LOH at 3p, 8p, 11p, 13q, 17p, 18q. TP53 is mutated in 30% of bladder cancers with a majority of G→A transitions at non-CpG sites and 2 hotspots at codons 280 and 285.

Cervical cancer**Disease**

Risk factors for cervical cancer include predominantly infection with certain human papillomaviruses such as HPV16 and HPV18. Carcinoma of the uterine cervix is one of the most common neoplasias among women worldwide.

Oncogenesis

The frequency of TP53 mutation in cervical cancer is very low. The p53 pathway is inactivated by the E6 protein that binds and inactivates the p53 protein. Rare TP53 mutations have been detected in HPV negative cancer.

Ovary carcinoma**Disease**

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies. The most important risk factor for ovarian cancer is a family history of a first-degree relative (mother, daughter, or sister) with the disease.

Oncogenesis

TP53 mutation is present in 20% in early stage to 80% in late stage ovarian cancers. The prognostic value of TP53 gene mutation is still a matter of debate, although positive IHC staining for p53 protein seems to be associated with poor prognosis.

Prostate cancer**Oncogenesis**

TP53 mutations are found in less than 20% of prostate cancers with a main hotspot at codon 273. Little is known about the role and prognostic value of these mutations.

Glioblastoma**Disease**

Glioblastoma is the most malignant astrocytic tumor and is preferentially located in the cerebral hemisphere. It may develop from a less malignant precursor lesion such as diffuse astrocytoma or anaplastic astrocytoma, or may develop de novo (secondary glioblastoma and primary glioblastoma respectively). Secondary glioblastoma are more frequent in younger patients and have a better prognosis.

Oncogenesis

TP53 mutation is an early and frequent (over 60%) event in secondary glioblastomas while it is rare in primary glioblastomas (inferior to 10%) with hotspots at codons 175, 248 and 273. TP53 mutation is associated with good prognosis as it is more frequent in secondary glioblastomas which occur in young patients and are of better prognosis.

To be noted

Note: Germinal mutations of P53 have also been found in families where the criteria for LFS or LFL were not reached.

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