

Gene Section

Review

P53 (Protein 53 kDa)

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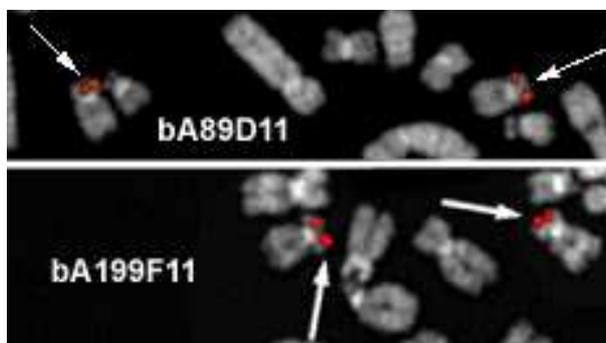
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Identity

Other names: TP53 (Tumour Protein 53)

HGNC (Hugo): TP53

Location: 17p13



Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

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; 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), postranslational 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 g) or apoptosis (by BAX, PUMA or NOXA). The cell growth arrest activity of p53 allow 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.

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; these mutations are missense (80%), non-sense (7.5%), deletions, insertions or splicing mutations (12.5%); there are some hot-spots for mutations at CpG dinucleotides at positions 175, 248, 273 and 282; P53 mutation is an adverse prognostic feature in a number of cancer, but not in all. Mutational events are related to carcinogen exposure in lung, liver and skin cancer.

Implicated in

Li-Fraumeni syndrome

Disease

Autosomal dominant condition; cancer prone disease; Li-Fraumeni syndrome is defined by the existence of both a proband with a sarcoma and two other first-degree relatives with a cancer by age 45 years; a germline mutation of P53 is found in at least 50% of cases; germline mutation of the kinase CHK2, an activator of p53, has been discovered in several Li-Fraumeni families free of p53 mutation.

Prognosis

Most common cancer in Li-Fraumeni children are: soft tissues sarcoma before the age of 5 yrs and osteosarcoma afterwards, and breast cancer in young adults; other frequent cancers: brain tumours, leukaemias, adrenocortical carcinoma; 1/3 of patients have developed more than one primary cancer, which is 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 yrs have had a cancer (i.e. penetrance is 50%, according to this disease definition); and penetrance is 90% at age 60 yrs.

Oncogenesis

(Known) germinal mutation are variable, but are mostly missense mutations located in exons 4 to 9 in tumours occurring in these patients, the other (wildtype) allele is lost, in accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

Haematological malignancies

Oncogenesis

P53 gene alterations have been found in: 20-30% of blast crisis CML (mostly in the myeloid type), often

associated with i(17q); in 5% of MDS cases and 15% of ANLL often with a visible del(17p); in 2% of ALL (but with high variations according to the ALL type, reaching 50% of L3 ALL (and Burkitt lymphomas); in 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), in 5-10% of multiple myelomas; in 60-80% of Hodgkin disease; in 30% of high grade B-cell NHL (rare in low grade NHL), and 50% of HIV-related NHL; P53 gene alterations in haematological malignancies are associated with a poor prognosis.

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; P 53 mutations, in this particular case, does not seem to have prognostic implication; P53 is mutated in 30% of lung adenocarcinomas to 80% of small cell lung carcinomas; hotspots at codons 157, 158, 179, 245, 248 and 273. p53 mutations in lung cancer from smoker have a very specific pattern related to carcinogen exposure (high frequency to GC->TA transversion and hot spot at codon 157 and 158).

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); P53 is mutated in 60-65% of colorectal cancer cases;

mutations of P53 are mostly located in exons 4 to 8 with hotspots at codons 175, 245, 248, 273 and 282.

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; P53 is mutated in 40-60% of bladder cancer cases; P53 mutations bear a prognostic implication.

Breast cancer

Prognosis

P53 mutation bears a prognostic implication in N+ patients and is related to poor response to doxorubicin therapy.

Oncogenesis

P53 is mutated in 30% of breast cancers; preferentially observed in advanced and aggressive forms; probably a late event; hotspots at codons 175, 248, and 273. The frequency and pattern of p53 mutation in breast cancer is subject to important geographical variations.

Skin cancers

Disease

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

Prognosis

Highly different according to the pathological group.

Oncogenesis

P53 is mutated in 40-60% of skin cancers; hotspots at codons 196, 248, 278. The pattern of p53 mutation in skin cancer is highly related to UV exposure.

Oesophagus cancers

Disease

Two main forms: squamous cell carcinoma and adenocarcinoma.

Oncogenesis

P53 is mutated in 50% of oesophagus cancers (70% in squamous cell carcinoma and 45% of adenocarcinoma); probably an early event; hotspots at codons 175, 248 and 273. The pattern of p53 mutation is different in squamous cell carcinoma and adenocarcinoma.

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

p53 mutation can be found in about 40-60% of gastric cancer. The prognosis of these mutations value is still a matter of debate.

Cervical cancer

Disease

Risk factor for cervical cancer includes 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 p53 mutation in cervical cancer is very low. The p53 pathway is inactivated by the E6 protein that binds and inactivates the p53 protein. Rare p53 mutations have been detected in HPV negative cancer.

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

p53 mutation can be found in about 40-60% of HNSCC cancer. The pattern of p53 mutation is related to carcinogen exposure. p53 mutation is an early event in this 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

Mutation of TP53 is the most common genetic alteration thus far in ovarian cancer, with mutations being present in approximately 50% of advanced stage ovarian carcinomas. The percentage of TP53 gene mutations is lower for endometrioid, mucinous and clear cell ovarian tumors, i.e. 28%, 16%, and 10% respectively. In patient with BRCA1 mutation, the frequency of p53 mutation is high (80%) with an unusual pattern of alteration not detected in sporadic ovarian cancer. P53 mutation is usually associated with a poor prognosis.

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

Mutations of p53 are very 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

p53 mutations observed in this highly chemoresistant tumour type.

Prostate cancer**To be noted****Note**

Germline mutations of P53 have also been found in families where the criteria for the Li-Fraumeni syndrome were not reached.

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