

Gene Section

Mini Review

P53 (Protein 53 kDa)

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Identity

Other names: TP53 (Tumour Protein 53)

Location: 17p13

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 phosphoprotein; contains, from N-term to C-term, a transactivation domain, a DNA-binding domain, nuclear localization signals and a tetramerization domain.

Expression

Widely expressed.

Localisation

Nucleus.

Function

Tumour suppressor gene; P53 is a transcriptional regulator acting as a guardian of the genome; in response to DNA damage, p53 is overexpressed and activates the transcription of genes such as p21 (implicated in cell-cycle arrest) and BAX (implicated in apoptosis); these activations allow either the cells to repair DNA damage before entering further in the cell cycle, or to be

eliminated. In both cases, the consequence is to prevent propagation of cells containing genetic alterations.

Homology

The five domains are highly-conserved regions between species.

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 tumor type to another; in general, mutations are found in the central part (exons 4-8) of the p53 gene; these mutations are missense, non-sense, deletions, insertions or splicing mutations; 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 types, but not in all.

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 mutation of P53 is found in at least 50% of cases; a percentage of mutations may be uncovered; a gene, upstream P53, could also be implicated in other cases with germline P53; therefore, heterogeneity is likely.

Prognosis

Most common cancer in Li-Fraumeni children are: soft tissues sarcoma before the age of 5 years 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 Blooms 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 mutation are variable, but are mostly missense mutations located in exons 5 to 8 (DNA binding domain); 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; P53 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, 179, 245, 248, and 273.

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; hotspot at codon 280; P53 mutations bear a prognostic implication.

Breast cancer

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.

Skin cancers

Disease

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

Prognosis

Highly different prognosis according to the pathological group.

Oncogenesis

P53 is mutated in 40-60% of skin cancers; hotspots at codons 196, 248, 278.

Oesophagus cancers

Disease

Two main forms: squamous cell carcinoma and adenocarcinoma.

Oncogenesis

P53 is mutated in 50% of oesophagus cancers (80% in squamous cell carcinoma); probably an early event; hotspots at codons 175, and 248.

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; hot spots otherwise at codons 249 and 273.

To be noted

Note

As above quoted, heterogeneity concerning the gene(s) mutated in Li-fraumeni is probable; on the other hand, germinal mutations of P53 have also been found in families where the criteria for the Li-Fraumeni syndrome were not reached.

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