I. CHROMOSOME INSTABILITY SYNDROMES

A handful of rare genetic diseases associate chromosome instability, DNA replication and/or repair anomalies, some shared clinical features, and an increased risk of cancer. These diseases are characterized by a high level of spontaneous chromatid breaks and chromosome rearrangements, and/or a hypersensitivity to clastogens (see an introduction to chromosomal aberrations). The genes implicated in these diseases are partly known and seem to have a role in DNA repair and/or in the cell cycle regulation. If lesions into DNA are not correctly repaired, mutations and rearrangements will accumulate, until, by chance, one of these mutations results in the activation of an oncogene or in the inactivation of the allele(s) of a tumor suppressor gene. Whence, chromosome instability syndromes are paradigmatic.

Fanconi Anemia (FA)
Autosomal recessive; q2 = 1/40 000.

Clinics:
- Growth retardation.
- Skin abnormalities: hyperpigmentation and/or café au lait spots.
- Skeletal malformations, particularly radius axis defects.
- Progressive bone marrow failure → bone marrow aplasia.

Neoplastic risk:
- Myelodysplasia and acute non lymphocytic leukemia: in 10% of cases; i.e. a 15000 fold increased risk; other cancers (5%).

Cytogenetics:
- Spontaneous chromatid/chromosome breaks.
- Hypersensitivity to the clastogenic effect of DNA cross-linking agents.
- Slowing of the cell cycle (G2/M transition).

Genes:
- 4 complementation groups; genes FACC, FA1

II. RETINOBLASTOMA / LI-FRAUMENI SYNDROME

III. HAMARTO-NEOPLASTIC SYNDROMES

I. CHROMOSOME INSTABILITY SYNDROMES

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Radiosensitivity:
- High sensitivity to radiations and to radiomimetic drugs.

Genes:
- Gene in 11q23: ATM probable role in DNA repair, recombinaison, and in the cell cycle control.

Note: Heterozygous for AT may be at increased risk of breast cancer.

Bloom Syndrome (BS)
Autosomal recessive; q2 = 2/100 000.

Clinics:
- Sun sensitive telangiectatic erythema.
- Dwarfismn.
- Normal intelligence.
- Combined immunodeficiency → infections.

Neoplastic risk
- Carcinomas (30%), lymphomas (25%), acute lymphocytic and non lymphocytic leukemias (15 % each), ...
- Mean age at first cancer onset: 21 yrs; more than one cancer in a given patient.

Cytogenetics:
- Spontaneous chromatid breaks.
- Diagnosis on the highly elevated spontaneous sister chromatid exchange rate (90 per cell).
- Slowing of the cell cycle (lenthening of the G1 and S phases).

Gene:
- Gene BLM , codes for a DNA helicase.

Xeroderma pigmentosum (XP)
Autosomal recessive; q2 = 0.4/100 000.

Clinics:
- Sun sensitiviromic lesions → skin cancers.
- Photophobia.
- Neurologic features.

Neoplastic risk:
- Multiple cutaneous and ocular tumors as early as from the age of 8 yrs (in sun exposed zones).

Cytogenetics:
- Normal level of breaks and chromatid exchanges.
- Hypermutability of the cells under UV irradiation.

Genes:
- 9 complementation groups. Genes ERCC (excision repair cross complemen) and XP (ex: XPAC): numerous and dispersed on various chromosomes; role in DNA repair (helicases) and in the complex repair/transcription factor.

II RETINOBLASTOMA and LI-FRAUMENI SYNDROME

These two diseases are examples of the involvement of tumor suppressor genes; they are also of interest for various reasons; retinoblastoma mixes constitutional and acquired chromosome features, the gene Rb is autosomal recessive but the disease appears to be autosomal dominantly inherited, due to rare events multiplied by numerous cells and conditional probabilities; Li-Fraumeni syndrome is a rare disease discovered from epidemiological studies, and P53 is, otherwise, THE gene involved in 50% of the cancers. Both genes are involved in the cell cycle regulation and arrest. If the cell cycle is not stopped until the background lesions into DNA are correctly repaired, mutations and rearrangements will accumulate along the cycles, until, by chance, one of these mutations results in the activation of an oncogene or in the inactivation of the allele(s) of a tumor suppressor gene.

Retinoblastoma
Cancer prone disease at increased risk of the cancer of the retina called (also) retinoblastoma
- Embryonic tumor of the neur ectoderma.
- Appears most often in childhood.
- There are sporadic forms (with a negative familly history) and hereditary forms.
- There are unilateral forms (mostly in the sporadic cases) and bilateral forms (mainly in the hereditary cases).
- Hereditary forms seem to be transmitted as an autosomal dominant disease with a 90 % penetrance.
- Patients having a retinoblastoma have an increased frequency of other cancers, in particular of osteosarcoma and pinealoma.
- In a (very) few cases, a visible chromosome 13 deletion may be seen on the constitutional karyotype, and, according to the lenght of the deletion, the patients present with dysmorphic features and mental impairment (as usual for unbalanced constitutional anomalies), in addition to the cancer(s) of the retina they have.
- These features are unusual, and some appear contradictory...

They will be explained by the two-step inactivation mechanism, according to AG Knudson (1971): both alleles of a tumor suppressor gene must be inactivated to let the cancer develop.
- 1st event : deletion
  - In a germ cell: hereditary form (therefore each of the cells of the patient, in particular each of the cells of each of the 2 eyes bear the deletion: that will considerably increase the risk of multiple retinoblastomas in 1 eye, or of bilateral retinoblastoma: conditional probability P(1st allele) X P(2nd allele) with the first proba already = 1).
  - or in a retinoblast: sporadic form.
- 2nd event: 2nd deletion: in a retinoblast (somatic deletion).
- Finally: when homozygosity for inactivation is reached → the tumor develops.

The gene is recessive; it however seems to be transmitted as an autosomal dominant disease in hereditary forms: the hereditary mutation, first event,
has a probability 1/2 to be transmitted to the "patient". If, by some means or other, the (second) somatic hit has a probability close to 1, then, the resulting probability to have a retinoblastoma will be 1/2 x 1 = 1/2, what is characteristic of autosomal dominant transmission. The somatic event's probability is close to 1 (the "some means or other" above noted is the result of the low rate of mutations multiplied by the great number of cells at risk). This somatic hit is produced either by:
- Loss of the normal chromosome 13 → monosomy with only the deleted 13 (hemizygosity).
- Loss of the normal chromosome 13 and duplication of the deleted 13 (homozygosity).
- Deletion within the normal 13 where "the important gene" sits.
- Mutation (or any other kind of inactivation) of "the important gene" present on the normal 13.

This gene has been called Rb, and belongs to the class of tumor suppressor genes (earlier "antioncogenes"), as, when they are normal and active, they prevent from cancer.

Rb: gene sitting in 13q14; 180 kb, 27 exons, mRNA of 4,7 kb \(\rightarrow\) P105 Rb protein: can form complexes with nuclear oncogenes; phosphorylated in S and G2/M phases of the cell cycle; unphosphorylated in G0 and G1 and associated with E2F; anti proliferative activity.

**LI-Fraumeni syndrome and P53**

1/3 of the population will have a cancer; Besides, exist familial cancers; more than a hundred genetic diseases are accompanied with an increased risk of cancers (either specific or pleiotropic).

In the general population, if a given person has a cancer: → risk is increased by 2 or 3 in the family. In certain types of familial cancers: → risk \(\times 10^7\) ! How to suspect an hereditary cancer:
- Too early in life;
- More than 1 cancer in 1 patient;
- Positive family history (other cancers, more than usual, in the family).

In 1969 FP Li and JF Fraumeni define a syndrome:
- Autosomal dominant,
- With: breast cancers, sarcomas, brain tumors, leukemias, ...
- Inclusion criteria: 1 individual having a sarcoma and at least 2 related persons with a sarcoma or a carcinoma.

**P53:**
- Gene sitting in 17p13; 20 kb, 11 exons (1st exon is non coding), mRNA of 3.0 kb.
- The protein presents a transactivation domain, a DNA-binding domain, nuclear localization signals and a tetramerization domain.
- Transcriptional regulator: in response to DNA damage, P53 activates the transcription of genes implicated in the cell-cycle arrest and genes implicated in apoptosis; these activations allow either the cells to repair DNA damage before entering further in the cell cycle, or to be eliminated.
- P53 is the most frequently (50%) mutated gene in cancers (with loss of fonction of the second allele) \((\text{SOMATIC MUTATION} = \text{ACQUIRED ANOMALY}).\)
- P53 is found mutated as an inborn condition in most (but not all!) patients with the congenital genetic disease named Li-Fraumeni syndrome \((\text{GERMINAL MUTATION} = \text{CONSTITUTIONNAL ANOMALY})\).

### III HAMARTO-NEOPLASTIC SYNDROMES

Hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; these diseases are heritable; hamartomas are benign proliferations that have a potential towards neoplasia; patients may also be at increased risk of benign and malignant tumors of other tissues and organs. The genes known so far are tumor suppressor genes, but no common fonction has yet been established.