Educational Items Section

Chromosomes, Leukemias, Solid Tumors, Hereditary Cancers

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Published in Atlas Database: February 2008

Online updated version: http://AtlasGeneticsOncology.org/Educ/Hempat_e.html

DOI: 10.4267/2042/44419

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Part I - Haematologic malignancies

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Introduction

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Introduction
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Introduction

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INTRODUCTION
Malignant blood diseases may be classified:
According to the clinical course:
- Chronic leukemias
- Acute leukemias
According to the lineage:
- Lymphoid lineage: B or T
- Myeloid lineage:
  - Myeloproliferative syndromes: quantitative anomalies.
  - Myelodysplastic syndromes: qualitative anomalies.
  - Acute myeloid leukemias (or acute non lymphoblastic leukemia).

According to the primary site:
- Leukemia: originates in the bone marrow; flows into the peripheral blood.
- Lymphoma: originates in the lymph nodes; invades bone marrow and blood.

Leukaemias are classified according to cytogentic, cytology and pathology, and immunophenotype of the malignant cells. The WHO (World Health Organization) classification has replaced the FAB classification of leukaemias.
I- MYELOPROLIFERATIVE SYNDROMES

Myeloproliferations: quantitive anomalies of the myeloid lineage.
- Chronic myelogenous leukaemia (CML)
- Polycytemia vera (PV)
- Idiopathic myelofibrosis (or agenogenic myeloid metaplasia)
- Essential thrombocytemia (ET)
- +/- Atypical chronic myelogenous leukemia (myelodysplastic/myeloproliferative disease)

I.1. Chronic myelogenous leukaemia (CML)

Malignant monoclonal process involving a pluripotent hematopoietic progenitor (therefore, most of the lineages are implicated).

Splenomegaly, high leukocyte count, basophilia, immature cells in the peripheral blood, low leucocyte alkaline phosphatase, bone marrow expansion with increased neutrophil lineage.

Prognosis: chronic phase, followed by blast crises, ending in an acute transformation; median survival was about 4 yrs before the recently introduced antityrosine kinase (imatinib mesylate) therapies.

Chromosome anomalies:
- t(9;22)(q34;q11).

Chromosome 22 appears shorter and was called Philadelphia chromosome (noted Ph).

Translocates a part of ABL1 (Abelson, 9q34) oncogene, next to a part of a particular DNA sequence of another oncogene, BCR (breakpoint cluster region), in 22q11 → production of a hybrid gene 5'BCR-3'ABL.

The normal ABL is transcribed, into a m-RNA of 6 to 7 kbases, which produces a protein (tyrosine kinase) of 145 kDalton with a low kinase activity.

The hybrid gene 5'BCR-3'ABL is transcribed into a mRNA of 8.5 kb, which produces a protein of 210 kDa with:

- an increased protein kinase activity
- an increased half-life, as compared to normal ABL.

In a percentage of cases, there is a variant/complexe translocation (e. g.: t(1;9;22)); the karyotype may even looks normal in some cases ("Ph" CML); however, it has been demonstrated by molecular technics that, whatever the variant translocation was, the hybride gene 5'BCR-3'ABL was always present (otherwise, it is NOT a CML!).

Therefore the translocation t(9;22) is the **specific anomaly** found in CML; however, this anomaly is not pathognomonic, as it may also be found in ALL or in rare AML cases.

Additional anomalies: most often, they are found at the time of the blast crisis, they may nonetheless be present at diagnosis; mainly: +/-Ph, and/or +8, and/or i(17q), and/or +19, and/or -7; Most often; these additional anomalies reflects the clonal evolution in various sub-clones.
Clonal evolution concept

Other myeloproliferative syndromes:

I.2. Polycytemia vera (PV)
- Red cell lineage mainly; median survival: 10 to 15 yrs.
- JAK2 (9p24) V617F mutation in 2/3 to 100% of cases → constitutive kinase activity.

I.3. Idiopathic myelofibrosis (or agnogenic myeloid metaplasia)
- Splenic metaplasia with progressive myelofibrosis; survival is very variable (3 to 15 yrs).
- JAK2 mutation in 50% of cases.

I.4. Essential thrombocythemia (ET):
- Megakaryocytic lineage mainly; survival = 10 yrs; chromosome anomalies are rare.
- JAK2 mutation in 1/2 to 1/3 of cases.

I.5. Atypical chronic myelogenous leukemia:
Hybrid genes, with the involvement of:
1- **PDGFRB** (5q33), or **FGFR1** (8p12), membrane associated tyrosine kinases which dimerize upon PDGF or FGF presence; role in signal transduction; and

2- A partner. +/- Non Hodgkin Lymphoma in the case of FGFR1 involvement → indicating that a stem-cell is likely to be implicated.
II- MYELODYSPLASTIC SYNDROMES (MDS)

II.1. Introduction
Myelodysplasia: cells look "bizarre", dysplastic.
Classified according to the FAB:
- Refractory anemia without excess of blasts (RA)
- Refractory anemia with excess of blasts (RAEB)
- Refractory anemia with ringed sideroblasts (RARS)
- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myelogenous leukemia (see above)
- Unclassifiable myelodysplasias
- Aside: Secondary myelodysplasias (see secondary acute leukemias).

Chromosome anomalies:
- del(5q) / -5
- del(7q) / -7
- + 8
- Various structural rearrangements.

II.2. Del(5q) and myeloid malignancies
It is the most common structural rearrangement in myelodysplastic syndromes (MDS) and in acute myeloid leukemias (AML); del (5q) is accompanied with given clinical and haematological features.

We herein summarize these three pictures as:
1- "the 5q− syndrome", with del(5q) as the sole karyotypic anomaly in MDS,
2- MDS with del(5q) and additional karyotypic anomalies, and
3- AML with del(5q) (solely or not).

Clinics:
1. The 5q− syndrome is a myelodysplastic syndrome (classified as refractory anemia (RA) in 75% of cases, RA with excess blasts (RAEB) in 15%).
   - Possibility of an exposure to a toxic agent in the environment.
   - Treatment: supportive; prognosis: favorable.
2. MDS with del(5q): de novo MDS and therapy-related MDS (with prior exposure to alkylating agent, with or without radiotherapy); RAEB or RAEBT (RAEB in leukemic transformation); CMML (chronic myelomonocytic leukemia).
   - Prognosis: unfavorable; median survival: 10-12 months.
3. AML with del(5q) solely (in 20-25% of cases) or not.
   - Phenotype: de novo AML and therapy-related AML; all FAB subgroups, mainly M2 AML.
   - Represents 15% of therapy-related AML with prior exposure to alkylating agents (with or without radiotherapy).
   - Prognosis: extremely poor; median survival: 3 months.

RPS14 (5q33), encoding for a ribosomal protein, was recently discovered (Jan 2008) has having a major role in the 5q− syndrome.
**III- ACUTE MYELOID LEUKAEMIAS (AML) (or Acute Non Lymphocytic Leukaemias (ANLL))**

**III.1. Introduction**

Massive proliferation of myeloid precursors; with a hiatus aspect in the maturation pyramid and entry of immature cells into the bloodstream. The new WHO/OMS classification replaces and completes the FAB classification (M1 to M7).

**FAB:**

- **M0**: Undifferentiated
- **M1**: myeloblastic without maturation
- **M2**: myeloblastic with maturation
- **M3**: promyelocytic
- **M4**: myelomonocytic
- **M5**: monocytic
- **M6**: erythroleukemia
- **M7**: megakaryoblastic

**WHO:**

First group: - AML with recurrent cytogenetic translocations

Second group: - Multilineage AML (mAML)

Third group: - Secondary AML

Fourth group: - others AML, Morphological and Immunophenotyping classification

Prognostic value of the chromosomal anomaly +++.

**III.2. First group: AML with recurrent cytogenetic translocations**

**III.2.1. t(8;21)(q22;q22):**

M2 mostly.

The most frequent anomaly in childhood AML; seen in children and adults; mean age 30 yrs.

Prognosis: Complete remission (CR) in most cases (90%); but relapse is frequent; and median survival: 1.5 yrs (adults) to 2 yrs (children).

**RUNX1** gene (alias: AML1, CBFA2) (21q22), transcription factor implicated in hematopoietic cell maturation; forms heterodimers with CBFB; formation of a hybrid gene; RUNX1 partner: RUNX1T1 (8q22).
III.2.2. t(15;17)(q25;q21):
- quasi pathognomonic of M3 AML
- RARA (17q12) (Retinoic acid receptor, alpha) genes, transcription factor implicated in hematopoietic cell maturation; formation of a hybrid gene; RARA partner: PML (15q22).
- Good prognosis (compared to others AML).
- Prognosis improvement due to recent differentiation therapy (all trans retinoic acid): Complete remission is obtained in 80-90% of cases.

III.2.3. inv(16)(p13q22):
- pathognomonic of M4eo-AML
- CBFB (16q22) gene, T-cell transcription factor, (forms heterodimers with RUNX1, see above); formation of a hybrid gene; CBFB partner: MYH11 (16p13).
- Good prognosis: median survival = 5 yrs.

III.2.4. 11q23 rearrangements:
- M4, M5, biphenotypic acute leukaemia
- MLL (11q23) is implicated: transcription regulator (yin/yang?), regulates (among others) HOX genes expression, → hematopoiesis and embryogenesis regulation; formation of a hybrid gene with a partner.
- Various rearrangements, of which are the t(9;11)(p22;q23), the t(11;19)(q23;p13.1), a partial duplication of MLL, ...
  - t(9;11)(p22;q23):
    - Phenotype: M5 most often (especially M5a), M4; de novo AML and therapy related AML with antitopoisomerase II drugs (epipodophyllotoxins, anthracyclins, actinomycin D).
    - Prognosis: CR in most de novo AML cases; the prognosis may not be as poor as in other 11q23 leukaemias, with a median survival around 4 yrs in de novo cases; very poor prognosis in secondary AML cases; MLL partner: MLLT3.
normal MLL (Editor 10/2005)
- AT hooks: 3 AT hooks, binding to the minor grove of DNA;
- SNL: 2 speckled nuclear localization signals;
- RD: repression domains RD1 and RD2:
  - RD1 or CXXC: cysteine methyl transferase, with a transcriptional repression activity;
  - RD2 recruits histone deacetylases HDAC1 and 2;
- PHD+bromo: 2 plant homeodomain, 1 bromodomain, and 1 plant homeodomain;
  - may be involved in protein-protein interaction;
- FYRN and the FRYC domains associate the p300/320 N-term protein called MLLn
  and the p180 C-term protein, called MLLc once MLL is cleaved by taspase 1 into these 2 proteins,
  before entering the nucleus.
  They form a multiprotein complex with of transcription factor TFII
- TAD: transactivation domains: binds CBP; may acetylates H3 and H4 in the HOX area.
- SET: SET domain: methyltransferase; methylates H3,
  including histones in the HOX area for allowing chromatin to be open to transcription.

MLLn / MLLc may have yin-yang functions.

MBR: major breakpoint region; breakpoints are clustered between exons 8 and 14

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MLL partners

III.2.5. Note:
Hundreds of chromosome rearrangements are not listed by the WHO in its "first group"; for example: t(9;22)(q34;q11) (very rare in AML; hybrid gene BCR-ABL1, poor prognosis).

III.3. Second group: Multilineage AML
This category is defined by the presence of multilineage dysplasia (in contrast with the t(15;17), for example, which affects only promyelocytes).

Chromosomes abnormalities:
del(5q) / -5

3q31-3q26 rearrangements:
- Phenotype: AML, often preceded by MDS; MDS may occur as an additional anomaly in CML with t(9;22), with thrombocytosis.
- Prognosis: median survival is only 4 mths.
- EVII (3q26): EVII and (antagonist?) MDS1-EVII splicing may play an important role in organogenesis, cell migration and differentiation; formation of a hybrid gene; partner: RPN1 (3q21).

del(7q) / -7
+8

Atlas Genet Cytogenet Oncol Haematol. 2009; 13(2)
Others ...

III.4. Third group: Secondary AML

III.4.1. Introduction

"Secondary " to exposure to toxins (ex: chemotherapy, radiotherapy, professional expositions (benzene), radiations, smoking.

Chromosomes anomalies:
- del(5q) / -5
- del(7q) / -7

after alkylating agent exposure, long-term latency (years).

- 11q23 (MLL) rearrangements.
- 21q22 (RUNX1) rearrangements.

Others after antitopoisomerase II exposure; short-term latency (often some months).

Very poor prognosis.

III.4.2. 11q23 rearrangements in therapy related leukaemias:

(Note: 11q23 rearrangements are also -and more often- found in de novo leukaemia)

Phenotype: these treatment related myelodysplasias (t-MDS) or treatment related leukaemias (t-AL) exhibit variable phenotypes:
- CMML or RAEB±T in MDS cases;
- AML most often (M4 or M5a mainly, M1, M2, M5b at times),
- ALL (and biphenotypic leukaemias), often CD19+, more rarely; t(4;11) cases are frequently ALL cases.

Etiology: 11q23 rearrangements in treatment related leukaemias were thought to be found mainly following a treatment with anti-topoisomerase II (epipodophyllotoxins) or with an intercalating topoisomerase II inhibitor (anthracyclins), as for some 21q22 rearrangements; actually, they may also be found after alkylating agents treatment and/or radiotherapy. The prior cancer is variable: breast cancer, non-Hodgkin lymphoma, Hodgkin disease, leukaemia, lung carcinoma, and other malignancies.

Epidemiology: up to 30% of t(11;19)(q23;p13.1), 10% or more of t(9;11), 5% of t(4;11) and 5% of t(10;11) are found in secondary leukaemias: altogether, 5 to 10% of 11q23 leukaemias are treatment related; these 11q23 second leukaemias are found at any age, from infancy to elder age.

Clinics: Latency before the outcome of the second leukaemia after the first cancer is often short (median 2 yrs), but highly variable, and may not depend on the type of treatment received; it is however most often shorter than in cases of second leukaemias associated with -5/del(5q) or with -7/del(7q).

Prognosis is poor, as in other therapy related leukaemias; in a recent excellent study (n=40), only 80% of patients achieved remission, æ relapsed within a year; median remission duration being 5 mths.

III.5. Fourth group: others AML, classified by Morphology and Immunophenotyping of the cells

AML M1 to M7, according to the FAB classification +M0 (undifferentiated) and biphenotypic acute leukaemias (AML + ALL)

IV- ACUTE LYMPHOBLASTIC LEUKEMIAS (ALL)

IV.1. Introduction

Heavy proliferation of B or T lymphoid precursors, The immunophenotyping (CD, Ig) allows the recognition of the lineage involved in the malignant process, and the degree of maturation of the malignant cell.

The cytology differentiates ALL1 and 2 on the one hand, and ALL3 with large Burkitt-type cells on the other hand.
MIC classification (Morphology, Immunophenotype, Cytogenetics) allows to define entities with given prognoses.
ALL often occur in childhood.

**Chromosomes anomalies:**

IV.2. t(4;11)(q21;q23)
- Immature (CD19+) B-cell.

- Occurs **often in childhood**, especially **very early** (e.g. congenital leukemia, before 1 yr);
- **Very poor prognosis** (median survival below 1 yr), the treatment being a bone marrow graft; genes MLL in 11q23 and AF4 in 4q21; formation of a hybrid gene.
IV.3. Other 11q23 rearrangements in leukemias

Phenotype:
de novo and therapy related leukemias; AML and
ALL grossly represent half cases each; MDS in the
remaining 5%; biphenotypic leukaemia at times; 11q23
rearrangements in treatment related leukaemias
represent 5-10% of 11q23 cases.

- MDS: most often RA or RAEB±T
- AML: M5a in half cases, M4 (20%), M1 or M5b
  (10% each), M2 (5%);
- ALL: B-cell mostly, L1 or L2, CD19+ in 60% of
  B-ALL cases, CD10+ 35%; T-ALL in rare cases
  (less than 1%);

Epidemiology: 25% are infant (less than 1 yr) cases;
children and adults each represent 50% of cases;
altogether, 11q23 rearrangements in childhood acute
lymphoblastic leukemia is frequent; M/F = 0.9 (NS)
Clinics: organomegaly; frequent CNS involvement
(5%); high WBC (above 50 x 10^9/l in 40%).

Prognosis very poor in general; variable according to
the translocation, the phenotype, the age, and whether
the leukaemia is de novo or secondary.

Cytogenetics:

- t(4;11)(q21;q23): represent 1/3 of cases.
- t(6;11)(q27;q23) : 5% of cases; mostly;
  children and young adults; male predominance.
- t(9;11)(p23;q23) : represent a of cases;
  myeloid lineage.
- t(10;11)(p12;q23) : 5% of cases; M4 or M5
  AML; ALL at times; from infants and children to
  (rare) adult cases.
- t(11;17)(q23;q21): rare; AML; not to be
  confused with the t(11;17)(q23;q21) in M3 AML.
- t(11;19)(q23;p13.1): 5% of cases; M4 or M5
  AML most often; de novo and therapy related AL;
  adult mainly; the gene involved in 19p13.1 is
  ELL a transcription activator.
- t(11;19)(q23;p13.3): 5% of cases; ALL,
  biphenotypic AL and AML (M4/M5 mainly);
  therapy related AL; T-cell ALL at times; these T-
  cell cases are the only cases of t(11;19) with an
  excellent prognosis; mostly found in infants (half
  cases), and other children (altogether: 70%), or
  young adults; the gene involved in 19p13.3 is
  MLLT1, a transcription activator.
- Various other poorly known 11q23
  rearrangements have been described.

How can be characterized a leukemia - Example given

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Cytology</th>
<th>FAB</th>
<th>Nb cases</th>
<th>Age</th>
<th>Sex (M/F)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;19)(q23;p13.3)</td>
<td>Pre B ALL</td>
<td>L1 (L2)</td>
<td>13</td>
<td>4m (15d - 8y)</td>
<td>5M / 7F</td>
<td>10 (0 - 90+)</td>
</tr>
<tr>
<td>Bi phenotypic</td>
<td>L2 (L1)</td>
<td>8</td>
<td>3m (1d - 8m)</td>
<td>1M / 7F</td>
<td>8 (0 - 34)</td>
<td></td>
</tr>
<tr>
<td>T-cell ALL</td>
<td>L1, L2</td>
<td>4</td>
<td>7y, 13y, 13y, 13y</td>
<td>1M / 3F</td>
<td>42+62+83+130+</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>M5, M4, M2</td>
<td>9</td>
<td>7m (0d - 10y)</td>
<td>8M / 1F</td>
<td>5 (0 - 160+)</td>
<td></td>
</tr>
<tr>
<td>t(11;19)(q23;p13.1)</td>
<td>AML</td>
<td>M4, M5, M2</td>
<td>14</td>
<td>49y (7d - 83y)</td>
<td>7M / 7F</td>
<td>6 (0 - 48+)</td>
</tr>
</tbody>
</table>

common features: high WBC
- Hybrid gene between: ETV6 (12p13), a transcription regulator, and RUNX1/AML1 (21q22), another transcription factor.

**IV.6. t(8;14)(q24;q32) and t(2;8)(p12;q24) and t(8;22)(q24;q11) variants**

- Pathognomonic of L3-ALL and Burkitt lymphoma (mature B malignant cell);
- The prognosis was poor until recently, where new treatments were accompanied with better outcome.
- MYC in 8q24; immunoglobulin heavy-chains (IgH), in 14q32, or light-chains K (IgL) in 2p12 and L (IgL) in 22q11: these translocations set the oncogene MYC under the regulation of immunoglobulin transcription-stimulating sequences (actives in the B-lineage), leading to overexpression. Note: there is NO hybrid gene.

**IV.7. 14q11 rearrangements**

ex: t(11;14)(p13;q11), t(8;14)(q24;q11) and t(10;14)(q24;q11)

- T cell. T-cell receptor (TCR D and A) belonging to the immunoglobulin superfamily in 14q11. These translocations set various oncogenes under the regulation of

T-cell receptor transcription-stimulating sequences (actives in the T-lineage, inactives in the B-lineage; such a translocation in the B-cell would remain silent, since these T-cell stimulating sequences are asleep in the B-cell), leading to overexpression. Note: there is NO hybrid gene.

**IV.8. B Cell/ T Cell**

- Hybrid gene between: ETV6 (12p13), a transcription regulator, and RUNX1/AML1 (21q22), another transcription factor.
IV.9. Others:

- del(6q). hyperploidy (hyperploidy under 50; hyperploidy above 50); they are of good prognosis.

- There are also good leukemias!:
  - dic(9;12)(p13;p13): childhood CD10+ ALL; PAX5 (9p13) / ETV6 (12p13); hybrid gene; Excellent prognosis.
IV.10. Domino game

Dominio Game 1

V.1. B-cell chronic lymphoproliferative disorders (CLD)

- Chronic lymphocytic leukemia (CLL):
  - Good prognosis in most cases.
  - +12, del(13q), del(11q) (ATM), del(17p) (TP53).
- Prolymphocytic leukemia: t(11;14)(q13;q32).
- Splenicular leukemia with villous lymphocytes: t(11;14)(q13;q32), del(7q), +3 ...
- Multiple myeloma: malignant monoclonal plasma cell proliferation.

V.2. B cell Non Hodgkin's lymphomas (NHL)

- Small lymphocytic lymphoma: +12, +3, del(6q)
- Follicular lymphoma (FL):
  - Small cleaved cells: good prognosis.
  - t(14;18)(q32;q21) BCL2 and IgH; the immunoglobulin gene enhancer stimulates the expression of BCL2; BCL2 is anti-apoptotic.
- Or: 3q27 rearrangements implicating BCL6, a transcription factor; the translocation partners of BCL6 are not confined to the immunoglobulin superfamily; the partner gene therefore fuses with BCL6.
- Diffuse large cell lymphoma 3q27 (BCL6) rearrangements.
- Burkitt's lymphoma (BL) (see above)
- Mantle cell lymphoma t(11;14)(q13;q32) (CCND1/IgH; the immunoglobulin gene

V- NON HODGKIN'S LYMPHOMAS / CHRONIC LYMPHOPROLIFERATIVE DISEASES
enhancer stimulates the expression of CCND1).

- **Marginal Zone B-cell lymphoma**
  \( t(11;18)(q21;q21) \) (BIRC3/MALT1 hybrid gene).

**V.3. T Cell:**

- T-cell prolymphocytic lymphoma
- Mycosis fungoides/Sezary’s syndrome
- Adult T-cell leukemia/lymphoma (ATLL)
- Anaplastic large cell lymphoma (ALCL)
  - \( t(2;5)(p23;q35) \); hybrid gene between NPM (2p23) and ALK (5q35).
  - Or ALK+ variants (with another partner).

  - ALK is a membrane associated tyrosine kinase receptor.
  - Note: ALK can also be implicated in the genesis of a rare solid tumor: the inflammatory myofibroblastic tumor. Moreover and strikingly, the hybrid gene and fusion protein can be identical in the lymphoma and in the myofibroblastic tumor (e.g. 5′ TP53 - 3′ ALK).
Part II - Solid Tumours

(short summary)

I. Sarcomas

II. Carcinomas with translocations

III. Carcinomas: colorectal cancer

IV. Carcinomas: breast cancer/ hereditary breast cancer

I- SARCOMAS

Sarcomas: it is an heterogeneous group, of many benign or malignant tumours, often the diagnostic is hard to reach; however, a number of these tumours present a specific translocation; which can be of great help for diagnostic ascertainement.

A few examples:

I-1. Lipoma: rearrangement of HMGA2 (12q15), high mobility group gene, non histone protein, architectural factor, preferential binding to AT rich sequences in the minor groove of DNA helix.

I-2. Liposarcoma: MDM2 amplification (NO translocation, NOR stimulation by a gene enhancer as for MYC) : (located in 12q15, MDM2 interacts with TP53 and RB1, inhibits the cell cycle arrest in G1 phase and apoptosis); Often, neighbouring genes too, CDK4 and HMGA2, may be amplified and over-expressed.

I-3. Inflammatory myofibroblastic tumor (see above).


I-5. Alveolar rhabdomyosarcoma: specific translocation t(2;13)(q35;q14); PAX3 (2q35, transcription factor implicated in proliferation, differentiation, apoptosis) and FKHR (13q14). Variant translocation: t(1;13)(p36;q14): PAX7(1p36) / FKHR.

I-6. Ewing's tumors / Primitive neurectodermal tumours (PNET): small round-cell tumours (difficult to diagnose) deriving from neural crests cells.

- t(11;22)(q24;q12) FLI1/ EWSR1 and variant translocations all implicating EWSR1.

- EWSR1 binds to RNA; repressor.

II- CARCINOMAS

II-1. There can be specific translocations, e.g.:

Papillary carcinoma of the Thyroid: RET (10q11, tyrosine kinase receptor) and partners hybrid genes.

Papillary renal cell carcinoma: TFE3, (Xp11, transcription factor) and partners hybrid genes.

Secretory Ductal Breast Carcinoma (rare, but ETV6/ NTRK3 hybrid gene, due to a t(12;15)(p13;q25)), a translocation also seen in Congenital Mesoblastic Nephroma, Congenital Fibrosarcoma, and - even more surprising - in a case of acute leukemia!

II-2. Most often, karyotypes are complex, and still poorly understandable; comparative genomic hybridization (CGH) and CGH array are particularly useful.

III- COLORECTAL CANCER model

The diploid form, RER+ (Replication Error +), sporadic, without loss of heterozygosity (LOH), with few TP53 and APC, mutations, in the right-sided colon.

The polypliod form, RER-, with LOH 5q, 17p, 18q, p53 mutations, more often in left-sided colon, with a poorer prognosis.

Colorectal cancers can also be related to given cancer-prone diseases:

III-1. Familial adenomatous polyposis (FAP): characterized by the development of hundreds of polyps at a very early age, due to mutations in APC (5q21); CTNNB1 is phosphorylated by a complex including APC, which leads to CTNNB1 degradation by the ubiquitin-proteasome; CTNNB1 is assumed to transactivate genes which may stimulate cell proliferation or inhibit apoptosis.

III-2. Hereditary nonpolyposis colon cancer (HNPPC) or Lynch syndrome: due to germline mutations in genes intervening in the repair of DNA mismatches occurring during replication (MSH2 and MLH1).

Adapted from Narayan et al. Molecular Cancer 2003
IV- BREAST CANCER model / HEREDITARY BREAST CANCER

Karyotype:
- complex, not yet understood.
- losses of heterozygocity (LOH)
- HSR (homogeneously staining region): → DNA amplification.

Genes Implicated:
- **ERBB2** (17q21, membrane-associated tyrosine kinase receptor), prognostic indicator. Overexpression of ERBB2 is associated with tumor aggressiveness; if ERBB2 is amplified, a treatment with Erceptin should be given,
- **HRAS, KRAS, NRAS** (GTP binding p21 proteins, signal transduction),
- **TP53**.
- **CCND1** (cell cycle control related to RB1),
- **FGFR1** (8p11, membrane associated tyrosine kinase),
- **BRCA1, BRCA2**.
- **PTEN** (10q23, phosphatase, downregulator of the PI3K/AKT pathway, also implicated in Cowden, a cancer prone disease),
- **ATM** (see below),
- **MSH2, MLH1, PMS1, PMS2, MSH3**, "Mismatch repair" genes,
- … etc…

… 5-10% of breast cancers are due to hereditary predisposition, with germinal mutations in:
- **BRCA1** (17q21; complex role: part of the DNA repair complex, transcriptional regulator, cell cycle regulator, role in apoptosis...)
- **BRCA2** (13q12, phosphorylated by ATM, implicated in the double-strand break response).

… Others hereditary conditions with predisposition to breast cancers:
- **Ataxia telangiectasia, Li-Fraumeni Syndrome**, etc… (see below).
Part III - Cancer prone diseases

I- Hereditary Breast Cancer, Colorectal Cancer, etc… (see above)

II- Chromosome Instability Syndromes

1. Fanconi Anemia (FA)
2. Ataxia telangiectasia (AT)
3. Bloom Syndrome (BS)
4. Xeroderma pigmentosum (XP)

III- Retinoblastoma / Li-Fraumeni Syndrome

1. Retinoblastoma
2. Li-Fraumeni Syndrome and TP53

IV- Hamarto-Neoplastic Syndromes

II- CHROMOSOME INSTABILITY SYNDROMES

Some rare genetic diseases:
- Fanconi Anaemia (FA)
- Ataxia Telangiectasia (AT)
- Bloom Syndrome (BS)
- Xeroderma pigmentosum (XP)

are defined by:
- chromosome instability, DNA repair anomalies and a
- High cancer frequency.

These diseases are defined by a high level of breaks or chromosomal rearrangements and/or a high sensibility to mutagen reagents.

If DNA lesions are not properly repaired, mutations and genes rearrangements fast accumulate, leading to oncogene activation or antioncogene inactivation, by chance, at a time or another.

II.1. Fanconi Anemia (FA)

Autosomal recessive; q² = 1/40 000.

Clinics:
- growth retardation
- skin abnormalities: hyperpigmentation
- or café au lait spots

- skeletal malformations, particularly radius axis defects
- progressive bone marrow failure → bone marrow aplasia

Neoplastic risk: myelodysplasia (MDS) and acute myeloid leukemia (AML): in 10% of cases; i.e. a 15 000 fold increased risk; other cancers (5%).

Cytogenetics:
- spontaneous chromatid/chromosome breaks.
- hypersensitivity to the clastogenic effect of DNA cross-linking agents.

Others: slowing of the cell cycle (G2/M transition).

Genes: At least 7 complementation groups; genes FANCA, FANCC, FANCD2…

The FA complex subsequently interacts in the nucleus with FANCD2 during S phase or following DNA damage.

Activated FANCD2, downstream in the FA pathway, will then interact with other proteins involved in DNA repair, possibly BRCA1; after DNA repair, FANCD2 return to the non-ubiquinated form.
### Physical Abnormalities in Fanconi's Anemia

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperpigmentation and, café au lait spots</td>
<td>77</td>
</tr>
<tr>
<td>Thumb anomalies</td>
<td>37</td>
</tr>
<tr>
<td>Other skeletal anomalies</td>
<td>29</td>
</tr>
<tr>
<td>Microsomy (small stature)</td>
<td>60</td>
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<tr>
<td>Low birth weight</td>
<td>56</td>
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<tr>
<td>Microcephaly</td>
<td>40</td>
</tr>
<tr>
<td>Renal anomalies</td>
<td>28</td>
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<tr>
<td>Hyposgenitalism</td>
<td>24</td>
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<tr>
<td>Strabismus</td>
<td>22</td>
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<tr>
<td>Microphthalmia</td>
<td>16</td>
</tr>
<tr>
<td>Hyporeflexia</td>
<td>19</td>
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<tr>
<td>Mental deficiency</td>
<td>17</td>
</tr>
<tr>
<td>Ear anomalies and, or deafness</td>
<td>7</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>6</td>
</tr>
</tbody>
</table>
II.2. Ataxia Telangiectasia (AT)  
Autosomal recessive; $q^2 = 1/40\,000$.  

**Clinics:**  
- telangiectasia: facial region exposed to sunlight.  
- progressive cerebellar ataxia.  
- combined immunodeficiency $\rightarrow$ infections $\rightarrow 80\%$ of deaths.  

**Neoplastic risk:** T-cell malignancies (a 70 fold and 250 fold increased risks of leukaemia and lymphoma respectively) $\rightarrow 20\%$ of deaths.  

**Cytogenetics:**  
- more than 10% of mitoses bear a chromosome rearrangement in 7p14, 7q35, 14q11, (localisations of receptor T genes, immunoglobulin superfamily) or 14q32.
Clonal rearrangements further occur → T-cell malignancy.

Others:
- Lentening of the cell cycle (slower S phase).
- Radiosensitivity: AT patients present a high sensitivity to radiations and to radiomimetic drugs.

Gene: ATM (11q22), key role in cell cycle control during double-strand DNA breaks; phosphorylate TP53, BRCA1, etc…

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

II.3. Bloom Syndrome (BS)
Autosomal recessive; $q^2 = 2/100 000$.

Clinical:
- Sun sensitive telangiectatic erythema.
- Dwarfism.
- 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).

Others: slowing of the cell cycle (lentening of the G1 and S phases).

Gene: BLM, (15q26), codes for a DNA helicase. Participates in a supercomplex of BRCA1-associated proteins named BASC (BRCA1-Associated genome Surveillance Complex) and

In a complex named BRAFT (BLM, RPA, FA, Topoisomerase IIIalpha) containing five of the Fanconia Anemia (FA) complementation group proteins (FANCA, FANCG, FANCC, FANCE and FANCF).
II.4. Xeroderma Pigmentosum (XP)
Autosomal recessive; $q^2 = 0.4/100000$.

**Clinics:**
- severe sun photosensitivity → poikilodermia, premature aging of the skin → 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.

**Others:** hypermutability of the cells under UV irradiation.

**Genes:** 9 complementation groups. Genes ERCC (excision repair cross complement) and XP (e.g.: XPA) : numerous and dispersed on various chromosomes; role in DNA repair (helicases) and in the complex repair/transcription factor.

All XP genes are implicated in various steps of the NER (nucleotide excision repair) system, except the XP variant that is mutated in a mutagenic DNA polymerase (POL H) able to bypass the UV-induced DNA lesions.

### III- RETINOBLASTOMA and LI-FRAUMENI SYNDROME

#### III.1. Retinoblastoma
Cancer prone disease at increased risk of the cancer of the retina called retinoblastoma.

- tumor of the neuroectoderm (retina).
- appears most often in childhood.
- there are sporadic forms (with a negative family 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 osteosarcoma.
• in a (very) few cases, a visible chromosome 13 deletion may be seen on the constitutional karyotype, and, according to the length of the deletion, retinoblastoma can either be isolated, or be a part of a malformative syndrome.

These features are unusual, and some appear contradictory...let's tell the story:

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 that of a bilateral retinoblastoma).
• 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.

Therefore, the gene is a recessive gene; however it seems to be transmitted with an autosomal dominant pattern in the hereditary forms; How?:

- The hereditary mutation, first event, has a probability of ½ to be transmitted from the carrier parent.
- The somatic event's probability is close to 1 (the probability of the somatic/second event is the result of the very low rate of mutation for each given cell multiplied by a great number of cells at risk).
- → so, the final probability to have a retinoblastoma, when one of the two parents is carrier, will be: 1/2 x nearly 1 = "nearly 1/2",
- ... which usually characterize autosomal dominant transmission (!).
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.

**RB1 (13q14)**
**Hereditary form:**
The left chrom. 13 carries a deletion concerning RB1. The right chrom. is normal.

- monosomy
- H 13 loss / deleted 13 duplication
- mitotic recombination
- deletion on the H 13
- inactivating mutation on the H 13
III.2. Li-Fraumeni Syndrome and TP53
- 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.
- In the general population, if a given person has a cancer: $\rightarrow$ the risk is increased by 2 or 3 in the family.
- In certain types of familial cancers: $\rightarrow$ risk x $10^3$.

**How to suspect an hereditary cancer predisposition:**
- too early in life;
- more than 1 cancer in 1 patient;
- positive family history.

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.

**Mutation of various genes can lead to Li-Fraumeni Syndrome:**
- TP53 in 70% of Li-Fraumeni cases, but also:
- CHK2 (22q12, role in DNA double-strand break response),
- PTEN (10q23, downregulator of PI3K/AKT pathway),
- CDKN2A (9p21, interacts with CDKs (cyclin dependent kinases), activates the cell cycle arrest by preventing RB1 phosphorylation).

...on the other hand, somatic mutations of P53 are found in about 50% of all cancers.

**IV- HAMARTO-NEOPLASTIC SYNDROMES**

Hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; hamartomas are benign proliferations that have a potential towards neoplasia; patients are at increased risk of benign and malignant tumors of various tissues and organs. These diseases are heritable; the genes known so far are tumor suppressor genes, but no common function has yet been established.
- Neurofibromatosis Type 1 (gene NF1)
- Neurofibromatosis Type 2 (gene NF2)
- Tuberous sclerosis
- Von Hippel-Lindau Syndrome (gene VHL)
- Multiple Endocrine Neoplasia type 1 (gene MEN1)
- Multiple Endocrine Neoplasia type 2 (gene RET, tyrosine kinase receptor, see above in "carcinomas with translocation")
- Cowden (gene PTEN, phosphatase, see "breast cancer" above). ...etc ...

... Example: NF1:
Neurofibromatosis Type 1
- Heredity: autosomal dominant with almost complete penetrance;
- frequency: 30/10^5 newborns (and 1 of 200 mentally handicapped persons): one of the most frequent genetically inheritable disease;
- Neomutation in 50%, mostly from the paternal allele;
- highly variable expressivity, from very mild to very severe; expressivity is also age-related.
- Clinics: NF1 is an hamartoneoplastic syndrome; hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; they are heritable malformations that have a potential towards neoplasia; the embryonic origin of dysgenetic tissues involved in NF1 is ectoblastic.
- Diagnosis is made on the ground of at least 2 of the following:
  - café-au-lait spots
  - 2 neurofibromas or 1 plexiform neurofibromas (mainly cutaneous)
  - 2 Lisch nodules (melanocytic hamartomas of the iris)
  - freckling in the axillary/inguinal region.
  - glioma of the optic nerve
  - distinctive bone anomalies (scoliosis, pseudoarthroses, bony defects (orbital wall)) ...
  - positive family history
  - Other features: macrocephaly, epilepsy, mental retardation in 10 %; learning disabilities in half patients, sexual precocity and other endocrine anomalies, hypertension (renal artery stenosis).
- Neoplastic risk:
  - 5% of patients having von Recklinghausen disease will have a cancer.
  - Neurofibromas (especially the plexiform variety) are polyclonal (benign) proliferation; may be present at birth or appear later. They may be a few or thousands, small or enormous, occur in the skin and in various tissues and organs.
  - Neurofibrosarcomatous transformation (malignant) of these in 5-10 %.
  - Schwannomas (optic nerve, see above), meningiomas, astrocytomas, ependymoma.
  - Childhood MDS (myelodysplasia) and AML, often with monosomy 7 (monosomy 7 syndrome , 'juvenile myelomonocytic leukaemia'): risk, increased by X 200 to 500,
most often before the age of 5 yrs; no increased risk of leukaemia in the adult.

- **Pheochromocytomas.**
- **Various other neoplasias**, of which are rhabdomyosarcomas.
- **Treatment**: early diagnosis, lifetime monitoring and surgery are essential.
- **Gene**: NF1 (neurofibromin 1) 17q11.2; (GTPase activating protein (GAP)) interacting with p21RAS → tumour suppressor.

**Mutations:**
- **Germinal**: deletions or insertions in 25% of cases, point mutations and translocations; no "cluster" of mutations, making difficult the diagnosis.
- **Somatic**: the second allele stays normal in benign tumours but is often lost in malignant tumours.

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This article should be referenced as such: