Scope

The Atlas of Genetics and Cytogenetics in Oncology and Haematology is a peer reviewed on-line journal in open access, devoted to genes, cytogenetics, and clinical entities in cancer, and cancer-prone diseases. It presents structured review articles ("cards") on genes, leukaemias, solid tumours, cancer-prone diseases, and also more traditional review articles ("deep insights") on the above subjects and on surrounding topics. It also present case reports in hematology and educational items in the various related topics for students in Medicine and in Sciences.

Editorial correspondence

Jean-Loup Huret
Genetics, Department of Medical Information,
University Hospital
F-86021 Poitiers, France
tel +33 5 49 44 45 46 or +33 5 49 45 47 67
jlhuret@AtlasGeneticsOncology.org or Editorial@AtlasGeneticsOncology.org

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PTCH (patched homolog)

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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Identity

Other names: PTC, but this term was confusing with PTC/PKA.
Location: 9q22.3
Local order: between FACC and XPAC.

DNA/RNA

Description
23 exons, 2 of which are non-coding; 34 kb.

Transcription
Alternate splicing: 3 different 5' termini.

Protein

Description
Glycoprotein; 12 transmembrane domains, 2 extra cellular loops and intracellular N-term and C-term.

Localisation
Transmembrane protein.

Function
Part of a signalling pathway; opposed by the hedgehog gene's product; transmembrane protein, with a probable cell to cell adhesion role; is thought to have a repressive activity on cell proliferation; the recent demonstration of NBCS syndrome (see below) as a chromosome instability syndrome suggests that this protein has a role in DNA maintenance, repair and/or replication.

Homology
Patched (drosophila segment polarity gene).

Mutations

Germinal
Germ-line mutations lead to protein truncation in naevoid basal cell carcinoma syndrome (NBCS) patients (see below).

Somatic
Mutation and allele loss events in basal cell carcinoma, in NBCS and in sporadic basal cell carcinoma are, so far, in accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

Implicated in

Naevoid basal cell carcinoma syndrome (NBCS) or Gorlin syndrome

Disease
Autosomal dominant condition; cancer prone disease (multiple basal cell carcinomas); it is also a chromosome instability syndrome.

Cytogenetics
Spontaneous and induced chromosome instability.

Sporadic basal cell carcinoma

References


This article should be referenced as such:
TAL1 (T-cell acute leukemia 1)

Jean-Loup Huret, Marie-Claude Labastie

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)
Institut d'Embryologie Cellulaire et Moléculaire-CNRS UPR 9064, Nogent-sur-Marne, France (MCL)

Identity
Other names: SCL (stem cell leukaemia), TCL5 (T-cell leukaemia 5).
Location: 1p32

DNA/RNA

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Description
8 exons; 16 kb.

Transcription
(Complex) alternate splicing of: 1A with 2A, or 3, or 5, vs 1B, 2B, 3 and 5.

Protein

Description
331 amino acids and other; 42, 40, 34 kDa; domains: prolin rich in N-term; basic Helix-Loop-Helix from the exon 6.

Expression
In erythroblasts, megakaryoblasts, mastocytes, basophils, and in the nervous system; role in haematopoietic cell differentiation.

Function
Transcription factor; exhibits sequence-specific DNA binding activity when in dimers with another bHLH protein such as E2A.

Homology
- TAL2 in 9q32;
- LYL1 in 19p13.

Implicated in

- t(1;14)(p32;q11)/T-ALL → TAL1/TCRD
- t(1;7)(p32;q34)/T-ALL → TAL1/TCRB

T-ALL with normal karyotype,

Deletions at the DNA level (in the 5' region) with a normal karyotype.

References


Ono Y, Fukuhara N, Yoshio O. Transcriptional activity of TAL1 in T cell acute lymphoblastic leukemia (T-ALL) requires RBTN1 or -2 and induces TALLA1, a highly specific tumor marker of T-ALL. J Biol Chem 1997 Feb 14; 272(7):4576-81.

This article should be referenced as such:
ALK (anaplastic lymphoma kinase)

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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Identity

Location: 2p23

DNA/RNA

Transcription

6.2 kb mRNA; coding sequence: 4.9 kb.

Protein

Description

1620 amino acids; 177 kDa; after glycosylation, produces a 200 kDa mature glycoprotein.

Expression

Tissue specific; mainly in: brain, gut and testis; not in the lymphocytes.

Localisation

Cell membrane.

Function

Membrane associated tyrosine kinase receptor; probable role in nervous system development and maintenance.

Homology

Homologies with the insulin receptor super family: LTK (leucocyte tyrosine kinase), TRKA, ROS (homolog of the drosophila Sevenless), IGF1-R and IRbeta.

Implicated in

\[ t(2;5)(p23;q35)/CD30+ \text{ NHL} \rightarrow \text{ NPM1}/\text{ALK} \]

Disease

High grade NHL; most often: CD30+ anaplastic large cell type.

Prognosis

Nonetheless, a 80% five yr survival may be associated with this anomaly.

Cytogenetics

Additional anomalies are most often found.

Hybrid/Mutated Gene

5' NPM1-3' ALK on der(5).

Abnormal Protein

680 amino acids; N-term NPM1 is fused to the 563 C-term aminoacids of ALK (i.e. the entire cytoplasmic portion of ALK); no apparent expression of the ALK/NPM1 counterpart; localisation: both in the cytoplasm and in the nucleus.

Oncogenesis

Via the kinase function activated by oligomerization of NPM1-ALK mediated by the NPM1 part.

References


This article should be referenced as such:

Gene Section
Short Communication

NF1 (neurofibromin 1)
Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France
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Identity
Location: 17q11.2

DNA/RNA
Description
60 exons; spans 350 kb; presence of 3 cryptic genes: OMGP, EVI2A, and EVI2B ('overlapping genes'), hidden within NF1 intron 27 with an opposite transcription direction.

Transcription
At least 4 alternate splicings; 9.0 mRNA complete cds; coding sequence: CDS 198..8717.

Protein
Description
The protein has been called neurofibromin; 2839 amino acids.
Expression
Is tissue and development stage specific.
Function
GTPase activating protein (GAP) interacting with p21\textsuperscript{RAS} \rightarrow tumour suppressor.
Homology
Other (GAP); IRA1 and 2, the yeast inhibitors of p21\textsuperscript{RAS}.

Mutations
Germinal
Large deletions or insertions in 25% of cases, translocations and point mutations; widely dispersed, with no cluster; yielding difficulties in diagnosis; truncating effect in 2/3 of cases.

Somatic
The second allele remains normal in benign tumours and is often lost in malignant tumours another process in tumourigenesis may involve RNA editing (for the second allele), which gives rise to a truncated neurofibromin having lost its GAP activity.

Implicated in
Neurofibromatosis type 1
Disease
Autosomal dominant cancer prone disease; neurofibromatosis type 1 (NF1: the same symbol is used for the disease neurofibromatosis type 1 and the gene neurofibromin 1) is an hamartoneoplastic syndrome.

Watson syndrome
Disease
Autosomal dominant disease with cardiac malformations, and, as is found in von Recklinghausen neurofibromatosis, low normal intelligence, café-au-lait spots, and neurofibromas but to a lesser extend.

Oncogenesis
In accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

References


This article should be referenced as such:
Childhood myelodysplastic syndromes

Jean-Loup Huret, Claude Léonard

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)

Cytogénétique, Laboratoire d'Anatomo Pathologie, CHU Bicêtre, 78 r Leclerc, F94270 Le Kremlin-Bicêtre, France (CL)

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Clinics and pathology

Disease

Very heterogeneous:

I. idiopathic MDS

II. secondary MDS: to previous chemo- and/or radio-therapy.

III. ‘genetic MDS’: cases associated with a congenital genetic disease, such as:

- Neurofibromatosis type 1 (Von Recklinhausen)(MIM 16220): an hamartoneoplastic syndrome,
- Kostmann syndrome (MIM 20270): also called congenital neutropenia,
- Bloom syndrome (MIM 21090): a chromosome instability syndrome,
- Dubowitz syndrome (MIM 22337): mimicks Bloom’s, but without chromosome instability,
- Fanconi anaemia (MIM 22765): a chromosome instability syndrome,
- Schwachman syndrome (MIM 26040): with pancreatic insufficiency, and risk of leukaemia,
- Pearson disease (MIM 26056) and other mitochondrial diseases: they often share pancreatic insufficiency, bone marrow pancytopenia with myelodysplastic features but maintained polyclonality, muscular and other ubiquitous manifestations,
- Familial monosomy 7,
- Familial platelet storage pool deficiency,
- Unbalanced constitutional karyotypes, including +21, +8, del(11q), del(21q) miscellaneous conditions.

Phenotype / cell stem origin

RA, RARS (very rare), RAEB, RAEBT, CML, 'Juvenile CML', 'Infantile Monosomy 7', ‘non classifiable cases according to the FAB’; with variable proportions according to the studies.

Epidemiology

10% of haematological malignancies in children; median age: 2 to 5 yrs; sex ratio: balanced for some, male predominance (in RAEB±T or CMML) for others.

Prognosis

CR is obtained; however, median survival is about 3 yrs, while 1/3 of the cases may be considered as cured; good prognostic features are: young age, female sex, normal karyotype, and some of the genetic predisposing factors; worse prognosis is found in secondary MDS, RAEB and RAEBT, cases with +8, +19, t(1;7).

Cytogenetics

Cytogenetics, morphological

A normal karyotype or a monosomy 7 (intermediate prognosis) are found in 30% - or more- of cases each; others are: +8, +21, t(1;7), del(6q).

References


[No authors listed]. Forty-four cases of childhood myelodysplasia with cytogenetics, documented by the Groupe Français de Cytogénétique Hématologique. Leukemia 1997 Sep; 11(9):1478-85.

This article should be referenced as such:

Atlas Genet Cytogenet Oncol Haematol. 1997; 1(1)
Idi(X)(q13)

Franck Viguié

Laboratoire de Cytogénétique - Service d'Hématologie Biologique, Hôpital Hôtel-Dieu, 75181 Paris Cedex 04, France

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Identity
**Clinics and pathology**

**Disease**
Acute non lymphocytic leukaemia (ANLL), Myelodysplastic syndromes (MDS), Chronic myeloproliferative diseases (MPS).

**Phenotype / cell stem origin**
M1, M2, M4 ANLL, often with preceding MDS; MDS: often RARS; an early progenitor cell is involved.

**Epidemiology**
Rare finding; only found in female patients aged 47-86 yrs; as one normal X chromosome seems to be needed, it is not that surprising that male cases are not found.

**Clinics**
No history of toxic exposure.

**Cytology**
Bone marrow iron accumulation, ringed sideroblasts are often found.

**Prognosis**
Variable.

**Genetics**

*Note:* The gene(s) involved are unknown; breakpoint located within a 450kb region proximal from XIST and containing an inverted repeat.

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**Cytogenetics**

**Cytogenetics, morphological**
Both the 2 centromeres appear to be active.

**Cytogenetics, molecular**
Breakpoint at or near the X inactivation center at Xq13. The XIST (X inactive specific transcript) gene is deleted. In 2 cases studied with BrDU, idic(X) was late-replicating.

**Additional anomalies**
+ idic(X)(or more copies) in 2/3 of cases; other known anomalies in MDS/ANLL; rings.

**References**


*This article should be referenced as such:*
Polycythemia vera (PV)
Jean-Loup Huret, Nicole Smadja

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)
Laboratoire de Recherche en Cytogénétique Hématologique, Hôpital Saint Antoine, Paris, France (NS)

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Clinics and pathology

Disease
Chronic myeloproliferative syndrome

Phenotype / cell stem origin
Pluripotent -non lymphoid- stem cell is involved.

Epidemiology
Annual incidence: 10/10^6; sex ratio: 1M/1F; median age 60 yrs.

Clinics
Asymptomatic for a long time, revealed by symptoms related to blood hyperviscosity (headache, vertigo...), or by asthenia, pruritus, skin erythrosis, or various other symptoms; splenomegaly is frequent: 70%; hepatomegaly in 40%; blood data: red cell mass of > 36 ml/kg in males, > 32 ml/kg in females; arterial oxygen saturation > 92%; high haemoglobin; WBC and platelets counts may be high.

Prognosis
Chronic disease, with, however, risks of thrombosis and haemorrhages in various tissues, including central nervous system; bone marrow evolution towards: 1-myelofibrosis with myeloid metaplasia (MMM) in 20% of cases; 2- acute leukaemia in 10%, either as an acute transformation, or as a therapy related ANLL; prognosis: median survival is 14 yrs with blood-letting, 12 yrs with 32P, less than 10 yrs with standard chemotherapy.

Cytogenetics

Cytogenetics, morphological
Normal karyotype is found in > 80% of cases at diagnosis, abnormal karyotype occurs with evolution, but the appearance of a clonal anomaly does not indicate progression of the disease, and may also occur during evolution to MMM; finally, up to 100% of cases with acute transformation have chromosome anomalies; these are: del(20q), +8, +9 may be seen solely or simultaneously in 20% of cases with chromosome anomalies, del(13q) and a partial duplication dup(1q)(sometimes in the form of t(1;7)(q10;p10) in 10%, other anomalies in 30%; none of them has prognostic significance; del(5q) and del(7q), hypodiploidy are seen in cases evolving towards therapy related ANLL; they confirm the diagnosis and indicate an adverse prognosis.

Genes involved and Proteins

Note: genes involved are unkown.

References

This article should be referenced as such:
Leukaemia Section
Short Communication

+11 or trisomy 11 (solely)
François Desangles
Laboratoire de Biologie, Hôpital du Val de Grâce, 75230 Paris, France

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Clinics and pathology

Disease
Myeloid lineage: (ANLL, MDS)

Phenotype / cell stem origin
M1, M2, and M4 ANLL; therapy related ANLL; MDS evolving towards ANLL; stem cell immunophenotype (DR+, CD34+, and CD15, 33 and/or 13 positive); trilineage dysplasia may be present.

To be noted that M1 and M2 subtypes of ANLL have rarely been found associated with the classical MLL rearrangements.

Epidemiology
Frequency: 1% of ANLL and MDS as well; balanced sex ratio; found in adults; med age: 60 yrs.

Prognosis
Short CR; poor prognosis.

Cytogenetics

Cytogenetics, morphological
+11

Cytogenetics, molecular
Partial tandem duplication (in situ) of MLL gene located in 11q23.

Probes
Oncor, Inc.

Additional anomalies
None (by that very fact).

Genes involved and Proteins

MLL
Location: 11q23
DNA / RNA
21 exons, spanning over 100 kb; 13-15 kb mRNA.

Protein
431 kDa; contains two DNA binding motifs (a AT hook, and Zinc fingers), a DNA methyl transferase motif, a bromodomain; wide expression; nuclear localisation; transcriptional regulatory factor.

Results of the chromosomal anomaly

Hybrid gene
Description
Exons 1 to 6 or 8 fused to a nearly entire MLL gene, starting at exon 2 (i.e. the duplicated segment is E2 to E6 or 8).

Fusion protein
Description
AT hook and DNA methyltransferase from MLL in N-term fused to a quite entire MLL in C-term.

Expression localisation
Nuclear localisation.

Oncogenesis
Probable altered transcriptional regulation.

To be noted
Such a tandem duplication of MLL may also be found in cases with a normal karyotype.

References

This article should be referenced as such:
**Chronic lymphocytic leukaemia (CLL)**

Hossein Mossafa, Jean-Loup Huret

Laboratoire Pasteur-Cerba, 95066, Cergy-Pontoise, France (HM)
Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)

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**Clinics and pathology**

**Disease**

Chronic lymphoproliferation

**Phenotype / cell stem origin**

B-cell disease; the existence of rare cases of T-CLL has been debated.

**Epidemiology**

Annual incidence 30/10^6; represents 70% of lymphoid leukaemias, 1/4 of all leukaemias; median age: 60-80 yrs, 2M/1F.

**Clinics**

Diagnosis is often delayed, due to the lack of symptoms (therefore, median survival from the beginning of the disease may be much more than med. surv. from diagnosis); enlarged lymph nodes; splenomegaly; blood data: lymphocytosis > 4 X 10^9/l; hypogammaglobulinemia in 60%.

**Cytology**

Typically, proliferation of mature small lymphocytes of normal morphology; lymphocytes with more abundant cytoplasm can be present; prolymphocytes must represent less than 10% of the lymphocytes (otherwise, the diagnosis of ‘chronic lymphocytic leukaemia-prolymphocytic leukaemia’ should be made); expression of sIg with monotypy (monoclonality); CD19+, CD20+, and CD5+ most often.

**Treatment**

None in early stage; chemotherapy afterwards.

**Evolution**

Unrelated causes and disease-related infections are the 2 major causes of death.

Other: autoimmune hemolytic anaemia and thrombocytopenia; transformation into Richter's disease or into prolymphocytic leukaemia (in 10%).

**Prognosis**

According to the staging: A (less than 3 lymph nodes, Hb < 10g/dl, platelets < 100 X 10^9/l): survival not reduced compared to age matched population; B (3 or more lymph nodes; Hb and platelets maintained): median survival of 5 yrs; C (Hb < 10g/dl and/or platelets < 100 X 10^9/l): median survival of 2 yrs; according to the karyotype: survival is better in cases with a normal karyotype (median: 15 yrs vs 8 yrs with an abnormal karyotype), worse in the 10% of cases where a complex karyotype is found (median: 6 yrs); specific chromosome anomalies have specific prognoses (see below).

**Cytogenetics**

**Cytogenetics, morphological**

Clonal anomaly is found in about 50% of cases; complex karyotypes are found in 10%; unrelated clones demonstrating the existence of cells subpopulations are frequent findings in this disease.

+12: is found in 15-20% of cases, depending on the use of interphase cytogenetics methods (FISH) and the cell morphology of the cases under study (trisomy 12 is typically found in atypical lymphocyte morphology and CD5- cases, often with an increased number of prolymphocytes, in advanced stages, and is associated with disease progression); trisomy 12 is an adverse prognostic factor (median survival: 5 yrs); found either as the sole anomaly, as an anomaly accompanied by others, or even as an accompanying (secondary) anomaly; present only in a subset of the malignant cell population; region q13-q22 might be of particular pathogenetic importance;
Chronic lymphocytic leukaemia (CLL)  
Mossafa H, Huret JL  

**Genes involved and Proteins**

Note: Genes involved as a primary event are still unknown. P53 has been found mutated in 10-15% of cases; adverse prognostic indicator.

**References**


This article should be referenced as such:  
Leukaemia Section
Short Communication

**dic(9;12)(p11-13;p11-12)**
Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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**Identity**

*Note:* dic(9;12) is mainly found in ALL, and that is the clinical entity which is described below.

**Clinics and pathology**

**Disease**
ALL most often; rarely: CML in blast crisis, T-cell leukaemia or lymphoma.

**Phenotype / cell stem origin**
Of dic(9;12)/ALL: L1/L2 CD10+ most often, may be CIg+ ALL.

**Epidemiology**
1% of paediatric ALL; sex ratio: 2M/1F; children and young adults (> 1 yr, < 25 yrs); no infant case.

**Clinics**
Moderate organomegaly; blood data: moderate WBC.

**Treatment**
No BMT; no high risk protocol.

**Prognosis**
CR in all cases; 5 yrs survival > 95%.

**Cytogenetics**

*Cytogenetics, morphological*
Dicentric with loss of parts of 9p and 12p → ploidy: 45 chromosomes.

**Additional anomalies**
+8, +21.

**To be noted**
Bone marrow transplantation should not be performed, as the prognosis of the dic(9;12)/ALL is excellent.

**References**


*This article should be referenced as such:*
t(1;3)(p36;q21)

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: August 1997

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Disease

Myeloid lineage (MDS, ANLL, therapy related ANLL, BC-CML)

Phenotype / cell stem origin

MDS (RA: 3 cases; RAEB: 4 cases; CMML: 2 cases; RAEBT: 1 case); ANLL (M1, M4...), often (13/16 cases) with preceding MDS, according to cases herein reviewed; seem to involve a myeloid stem cell, t(1;3) being absent from B or T lymphocytes; may be secondary to toxic exposure.

Epidemiology

Median age: 49 yrs; sex ratio: 7M/9F.

Clinics

Blood data: frequent thrombocytosis.

Cytology

Dysmegakaryocytopoiesis.

Prognosis

Very poor so far: median survival is 6 mths in ANLL, 20 mths in MDS.

Clinics and pathology

Cytogenetics

Additional anomalies

del (5q) in 3 of 16 cases.

To be noted

This translocation share commun features with inv(3)(q21q26), t(3;3)(q21;q26), and t(3;5)(q21-25;q31-35).

References


This article should be referenced as such:

**Identity**

\[ t(1;22)(p13;q13) \] G- and R- banding

**Clinics and pathology**

**Disease**

Only found so far in M7 ANLL (acute megakaryocytic leukaemia); not found in Down syndrome (DS), and yet, DS is a disease with highly elevated risk of M7.

**Phenotype / cell stem origin**

M7 (CD 41).

**Epidemiology**

30% of paediatric M7; 70 to 100% of infants M7; age: infants (17/18); sex ratio: 5M/13F herein reviewed.

**Clinics**

Organomegaly; blood data: moderate WBC; Thrombocytopenia; myelofibrosis.

**Prognosis**

CR: 11/18; poor survival is probable.

**Cytogenetics**

**Additional anomalies**

Often none; otherwise: +der(1), +19, +6…

**References**


Lion T, Haas OA. Acute megakaryocytic leukemia with the \( t(1;22)(p13;q13) \). Leuk Lymphoma 1993 Sep; 11(1-2):15-20. (Review).

This article should be referenced as such:

t(3;5)(q25;q34)
Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: August 1997

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Clinics and pathology

Disease
ANLL; may be preceded by MDS; BC-CML

Phenotype / cell stem origin
M2, M4, M6 (although a rare subtype) ANLL; trilineage involvement.

Epidemiology
Med. age: 35 yrs; balanced sex ratio.

Prognosis
CR: 8/12, but median survival is less than 1 yr.

Results of the chromosomal anomaly

Hybrid gene
Description
5′ NPM-3′ MLF1 on der(5).

Expression localisation
54 kDa with the 175 N-term amino acids from NPM; localization: nucleus, mainly in the nucleolus.

Cytogenetics

Cytogenetics, morphological
Location of breakpoints is difficult to ascertain.

Additional anomalies
Most often none; +8.

Genes involved and Proteins

MLF1
Location: 3q25
Protein
31 kDa; do not contain known functional motifs; widely expressed; cytoplasmic localisation.

NPM1
Location: 5q34
Protein
Nuclear localisation; binds to single and double strand nucleic acids; phosphoprotein that may transport ribonucleoproteins; may also have a role in DNA replication.

To be noted
Specific comments: this translocation share some (but not all) common features with t(1;3)(p36;q21), inv(3)(q21q26)..., although the genes involved on chromosome 3 are different.

References

This article should be referenced as such:
t(12;21)(p12;q22)
Jean-Loup Huret, Alain Bernheim

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH);
Laboratoire de Cytogénétique, UMR 1599 CNRS, Institut Gustave Roussy, 94805 Villejuif, France (AB)

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Clinics and pathology

Disease
B cell ALL

Phenotype / cell stem origin
L1 and L2, CD10+.

Epidemiology
15 to 35% of paediatric B-lineage ALL: so far the most frequent translocation in this group; rare or absent in adults and in infants; age: children; no case > 20 yrs so far; male and female equally represented.

Clinics
Standard ALL.

Prognosis
CR in all cases; prognosis seems good.

Cytogenetics

Cytogenetics, morphological
t(12;21) often remained undetected.

Cytogenetics, molecular
Easily detected by chromosomes 12 and 21 painting or specific probes.

Additional anomalies
Frequent del(12)(p12) on the other chromosome; in rare cases duplication of der(21)t(12;21); looks like a +21.

Variants
t(6;12;21), t(3;12;21)

Genes involved and Proteins

ETV6
Location: 12p13
DNA / RNA
9 exons; alternate splicing.

Protein
Contains a HLH domain and a ETS-DNA binding domain; wide expression; nuclear localisation; ETS-related transcription factor.

AML1
Location: 21q22
DNA / RNA
Transcription is from telomere to centromere.

Protein
Contains a Runt domain and, in the C-term, a transactivation domain; forms heterodimers; widely expressed; nuclear localisation; transcription factor (activator) for various hematopoietic-specific genes.

Results of the chromosomal anomaly

Hybrid gene

Description
TEL-AML1 chimaeric gene; 5’ centromere to 3’ telomere orientation.

Transcript
The fusion transcript on chromosome 21 TEL-AML1 is the crucial one; the AML1-TEL transcript is absent in some cases; the other TEL allele is often deleted.
Detection protocol
RT-PCR of the fusion transcript.

Fusion protein
Description
Helix loop helix of TEL fused to the nearly entire AML1 protein, comprising the Runt domain and the transactivation domain.

References


This article should be referenced as such:
+14 or trisomy 14 (solely)
Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: August 1997

Online version is available at: http://AtlasGeneticsOncology.org/Anomalies/tri_14.html
DOI: 10.4267/2042/32032

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Clinics and pathology

**Disease**
Myeloid disorders: MDS in more than half cases, ANLL in 1/4 of cases, chronic myeloproliferative syndrome (atypical CML); exceptionally: lymphoproliferations; therefore, only trisomy 14 solely in myeloid malignancies is herein described.

**Phenotype / cell stem origin**
MDS: RA, RAEB±T mainly; ANLL: M1, M2, M4; atypical CML with dysplastic features.

**Epidemiology**
Median age 60-65 yrs (range: 4-89 yrs); sex ratio: 4M/3F.

**Clinics**
No history of carcinogen exposure of note; blood data: platelets count: 130 X 10^9/l; monocytosis in half cases.

**Cytology**
All FAB subtypes of MDS can be found; atypical CML cases present with dysplastic features; non-lobulated megakaryocytes are often found.

**Prognosis**
Survival < 2 yrs in most cases; +14 do not seem to bear a distinct prognosis.

**Cytogenetics, molecular**
Chromosome painting (although +14 detection attempts are, so far, not relevant).

**Additional anomalies**
None, at least in the sub-clone with ‘+14 solely’, by that very fact; most often none in karyotype follow-up.

**Variants**
May be found as i(14q).

**Genes involved and Proteins**

Note: genes involved are unknown.

References


This article should be referenced as such:
t(3;12)(q26;p13)
François Desangles

Laboratoire de Biologie, Hôpital du Val de Grâce, 75230 Paris, France

Published in Atlas Database: September 1997

Online version is available at: http://AtlasGeneticsOncology.org/Anomalies/t0312.html
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Identity

![G-banding](image)

Clinics and pathology

**Disease**
Myeloid lineage: MDS in transformation, ANLL, BC-CML.

**Phenotype / cell stem origin**
Multilineage involvement; RAEB → M2, M7 and others ANLL subtypes.

**Epidemiology**
Only 8 cases described so far; sex ratio: 3M/1F; age: 3-87 yrs (med: 40 yrs).

**Cytology**
Megakaryocytes dysplasia

**Prognosis**
Very poor; survival often below 1 yr.

Cytogenetics

**Cytogenetics, molecular**
Heterogenous breakpoints.

**Probes**
- EVI1: ly2 and 13 E Parganas, St Jude Children's Research Hospital, Memphis, TN;
- MDS1: P856 G Nucifora, Univ. of Chicago, IL;
- TEL: YAC 958b8 CEPHI Mega-YAC library Paris, France;
- TEL: cDNA c50F4, c163E7, c148B6 Lawrence Livermore National Laboratories, Livermore, CA.

**Additional anomalies**
del(7q) or -7.

**Genes involved and Proteins**

**MDS1**

**EV11**
Location: 3q26

**ETV6**
Location: 12p13

DNA / RNA
9 exons; alternate splicing.

**Protein**
Contains a Helix-Loop-Helix and ETS DNA binding domains; wide expression; nuclear localisation; ETS-related transcription factor.

**References**


This article should be referenced as such:
t(8;21)(q22;q22)
Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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Identity

t(8;21)(q22;q22) G-banding (left) - Courtesy Jean-Luc Lai and Alain Vanderhaegen (top) and Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap Cytogenetics at the Waisman Center (middle and below); R-banding (right) - above: Editor; 2nd row: - Courtesy Christiane Charrin; 3rd and 4th row: - Courtesy Roland Berger.

Clinics and pathology

Disease
ANLL

Phenotype / cell stem origin
M2 mostly, rarely: M1 or M4.

Epidemiology
Annual incidence: 1/10^6; 10% of ANLL, 40% of M2
ANLL; the most frequent anomaly in childhood ANLL; Seen in children and adults; mean age 30 yrs, rare in elderly patients; male excess (4M/3F) is much less than sometimes claimed.

Clinics
Chloromas
Cytology
Numerous and thin Auer rods; eosinophilia of the bone marrow; CD19 (early B) and CD56 (natural killer) may be expressed: the cell involved may be an early progenitor.

Prognosis
CR in most cases (90%); but relapse is frequent, and median survival -1.5 yrs (adults) to 2 yrs (children)- in the range with other ANLL in some series, relatively long median survival, especially in the adults for others; no adverse effect of additional chromosome anomalies.

Cytogenetics

Cytogenetics, molecular
Cases with cryptic molecular translocation have been detected (similar to Ph negative CML with positive BCR-ABL) → FISH use may be relevant.

Additional anomalies
Sole anomaly in only 20%; additional anomalies: numerical in 2/3, structural in 1/3; loss of Y or X chromosome in half cases (1 X must be present), del(7q) or -7, +8, del(9q): 10% each.

Variants
Complex t(8;21;Var) involving a (variable) third chromosome have been described in 3%; part from chromosome 21 goes on der(8), part of the 8 on der (Var), and part of Var on der(21); therefore, the crucial event lies on der(8).

Translocation t(8;21) is found in 5-12% of AML. Among the non-random chromosomal aberrations observed in AML, t(8;21)(q22;q22) is one of the best known and usually correlates with AML M2, with well defined and specific morphological features. The common morphological features include the presence of large blast cells with abundant basophilic cytoplasm, often containing numerous azurophilic granulations; few blasts in some cases show very large granules (pseudo-Chediak-Higashi granules), suggesting abnormal fusion. Auer rods are frequently found. In addition to the large blast cells, there are also some smaller blasts, predominantly found in the peripheral blood. Promyelocytes, myelocytes and mature granulocytes with variable dysplasia are seen in the bone marrow. These cells may show abnormal nuclear segmentation and/or cytoplasmic staining defects including homogeneous pink colored cytoplasm - Courtesy Georges Flandrin, CD-ROM AML/MDS G. Flandrin/ICG. TRIBVN.
Genes involved and Proteins

**ETO**

Location: 8q22

DNA / RNA

Transcription is from telomere to centromere.

Protein

3 proline rich domains, 2 Zn fingers, and in C-term, a PEST region; tissue restricted expression; nuclear localisation; putative transcription factor.

**AML1**

Location: 21q22

DNA / RNA

Transcription is from telomere to centromere.

Protein

Contains a Runt domain and, in the C-term, a transactivation domain; forms heterodimers; widely expressed; nuclear localisation; transcription factor (activator) for various hematopoietic-specific genes.

Results of the chromosomal anomaly

**Hybrid gene**

Description

5’ AML1 - 3’ ETO; breakpoints: at the very 5’ end of ETO, between exons 5 and 6 in AML1.

Detection protocol

RT-PCR in cases: 1- of typical cell morphology, but apparently without the t(8;21); 2- for minimal residual disease detection.

**Fusion protein**

Description

The N-term runt domain from AML1 is fused to the 577 C-term residues from ETO; reciprocal product not detected; probable DNA binding role; the fusion protein retains the ability to recognize the AML1 consensus binding site → negative dominant competitor with the normal AML1) and to dimerize with the CBFb subunit.

Oncogenesis

Probable altered transcriptional regulation of normal AML1 target genes.

References


This article should be referenced as such:

t(9;22)(q34;q11) in ALL

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: September 1997

Online version is available at: http://AtlasGeneticsOncology.org/Anomalies/t0922ALL.html

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Identity

Note: Although the same hybrid genes issued from ABL and BCR are the hallmark of the t(9;22) translocation, this translocation may be seen in the following diseases: CML, ANLL, and ALL and will therefore be described in the 3 different situations: t(9;22)(q34;q11) in CML, t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL. t(9;22)(q34;q11) in ALL is herein described.
**Clinics and Pathology**

**Disease**
ALL

**Phenotype / cell stem origin**
L1 or L2 ALL; most often with B-cell phenotype, rare T-cell cases; heterogeneity of lineage involvement: may either be a multipotent stem cell, or a lymphoid-committed progenitor.

**Epidemiology**
20% of adult ALL, 2-5% of children ALL.

**Clinics**
Frequent CNS involvement, even at diagnosis; blood data: high WBC (50-150 x 10^9/l).

**Cytology**
CD10+ in most cases, sometimes CD19+ CD10-.

**Treatment**
BMT is indicated.

**Prognosis**
Is very poor, especially in lymphoid-committed progenitor cases; the breakpoint in M-bcr or in m-bcr (see below) does not seem to have impact on prognosis.

**Cytogenetics**

**Cytogenetics, morphological**
The chromosomal anomaly disappears during remission, in contrast with BC-CML cases when treated with conventional therapies.

**Cytogenetics, molecular**
Is useful to uncover a 'masked Philadelphia' chromosome, where chromosomes 9 and 22 all appear to be normal, but where cryptic insertion of 3' ABL within a chromosome 22 can be demonstrated.

**Additional anomalies**
Found in 50 to 80% of cases: +der(22), -7, del(7q) most often, +8, but not an i(17q), in contrast with CML and ANLL cases; complex karyotypes, often hyperploid, are frequent.

**Variants**
t(9;22;V) and apparent t(V;22) or t(9;V), where V is a variable chromosome, may be found, as in CML.

**Genes involved and Proteins**

**ABL**

**Location:** 9q34

**DNA / RNA**
Alternate splicing (1a and 1b) in 5'.

**Protein**
Giving rise to 2 proteins of 145 kDa; contains SH (SRC homology) domains; N-term SH3 and SH2 - SH1 (tyrosine kinase) - DNA binding motif - actin binding domain C-term; widely expressed; localisation is mainly nuclear; inhibits cell growth.

**BCR**

**Location:** 22q11

**DNA / RNA**
Various splicings.

**Protein**
Main form: 160 kDa; N-term Serine-Threonine kinase domain, SH2 binding, and C-term domain which functions as a GTPase activating protein for p21rac; widely expressed; cytoplasmic localisation; protein kinase; probable role in signal transduction.

**Results of the chromosomal anomaly**

**Hybrid gene**

**Description**
The crucial event lies on der(22), id est 5' BCR/3' ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed;
- breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5' of 1b, or 3' of 1a, but always 5' of exon 2;
- breakpoint in BCR is either:
  1- in the same region as in CML, called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210), with the first 902 or 927 amino acids from BCR;
  2- in a 35 kb region between exons 1 and 2, called m-bcr (minor breakpoint cluster region), → 7 kb mRNA, resulting in a 190 kDa protein (P190), with the 427 N-terminal amino acids from BCR.

**Transcript**
7 or 8.5 kb.
**Fusion protein**

**Description**

190 or 210 kDa (see diagram); BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear; this may have a carcinogenetic role.

The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hiding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated.

**Oncogenesis**

1-Proliferation is induced: there is activation by BCR/ABL of Ras signal transduction pathway via it's linkage to son-of-sevenless (SOS), a Ras activator; PI3-K (phosphatidyl inositol 3' kinase) pathway is also activated; MYC as well; 2-BCR/ABL inhibits apoptosis; 3-BCR/ABL provokes cell adhesive abnormalities: impaired adherence to bone marrow stroma cells, which allows unregulated proliferation of leukaemic progenitors.

**To be noted**

Blast crisis is sometimes at the first onset of CML, and those cases may be undistinguishable from true ALL with t(9;22) and P210 BCR/ABL hybrid.

**References**


This article should be referenced as such:

Leukaemia Section
Mini Review

**t(9;22)(q34;q11) in ANLL**

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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**Identity**

Note: Although the same hybrid genes issued from ABL and BCR are the hallmark of the t(9;22) translocation, this translocation may be seen in the following diseases: CML, ANLL, and ALL, and will therefore be described in the 3 different situations: t(9;22)(q34;q11) in CML, t(9;22)(q34;q11) in ALL, t(9;22)(q34;q11) in ANLL.

**t(9;22)(q34;q11) in ANLL** is herein described.

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**t(9;22)(q34;q11) G-banding (left)** - Courtesy Jean-Luc Lai and Alain Vanderhaegen (3 top) and Diane H. Norback, Eric B. Johnson, and Sara Morrison-Delap, UW Cytogenetic Services (2 bottom); **R-banding (right) top** Editor; **2 others** Courtesy Jean-Luc Lai and Alain Vanderhaegen; **diagram and breakpoints (Editor)**.
Clinics and pathology

**Disease**
ANLL

**Phenotype / cell stem origin**
Mostly M1 or M2 ANLL.

**Epidemiology**
3% of ANLL; 1% in childhood ANLL.

**Prognosis**
Is very poor.

Cytogenetics

**Cytogenetics, morphological**
The chromosomal anomaly disappears during remission, in contrast with BC-CML cases when treated with conventional therapies.

Genes involved and Proteins

**ABL**
Location: 9q34

DNA / RNA
Alternate splicing (1a and 1b) in 5'.

Protein
Giving rise to 2 proteins of 145 kDa; contains SH (SRC homology) domains; N-term SH3 and SH2 - SH1 (tyrosine kinase) - DNA binding motif - actin binding domain C-term; widely expressed; localisation is mainly nuclear; inhibits cell growth.

**BCR**
Location: 22q11

DNA / RNA
Various splicings.

Protein
Main form: 160 kDa; N-term Serine-Treonine kinase domain, SH2 binding, and C-term domain which functions as a GTPase activating protein for p21rac; widely expressed; cytoplasmic localisation; Protein kinase; probable role in signal transduction.

Results of the chromosomal anomaly

**Hybrid gene**

**Description**
The crucial event lies on der(22), id est 5' BCR/3' ABL hybrid gene is pathogenic, while ABL/BCR may or may not be expressed; Breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5' of 1b, or 3' of 1a, but always 5' of exon 2; Breakpoint in BCR is either (as in ALL cases):
1- in the same region as in CML, called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210), with the first 902 or 927 amino acids from BCR;
2- in a 35 kb region between exons 1 and 2, called m-bcr (minor breakpoint cluster region), → 7 kb mRNA, resulting in a 190 kDa protein (P190), with the 427 N-terminal amino acids from BCR.

**Transcript**
7 or 8.5 kb
**Fusion protein**

**Description**

190 or 210 kDa (see diagram); BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear; this may have a carcinogenetic role. The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hiding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated.

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1-Proliferation is induced: there is activation by BCR/ABL of Ras signal transduction pathway via it's linkage to son-of-sevenless (SOS), a Ras activator; PI3-K (phosphatidyl inositol 3' kinase) pathway is also activated; MYC as well; 2-BCR/ABL inhibits apoptosis; 3-BCR/ABL provokes cell adhesive abnormalities: impaired adherence to bone marrow stroma cells, which allows unregulated proliferation of leukaemic progenitors.

**To be noted**

Blast crisis is sometimes at the first onset of CML, and those cases may be undistinguishable from true ANLL with t(9;22) and P210 BCR/ABL hybrid.

**References**


This article should be referenced as such:

Solid Tumour Section
Mini Review

Bladder cancer
Jean-Loup Huret, Claude Léonard

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)
Cytogénétique, Laboratoire d’Anatomo Pathologie, CHU Bicêtre, 78 r Leclerc, F94270 Le Kremlin-Bicêtre, France (CL)

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Classification

Existence of different histologic types.
Very rare types are:
- Squamous cell carcinoma (5%);
- Adenocarcinoma (2%);
- The most frequent, representing 90-95% of cases is transitional cell carcinoma of the bladder, herein described.

Clinics and pathology

Disease
Cancer of the urothelium

Epidemiology
Annual incidence: 250/10^6, 2% of cancers, the fourth cancer in males, the seventh in females, 3M/1F; occurs mainly in the 6th-8th decades of life; risk factors: cigarette smoking and occupational exposure (aniline, benzidine, naphtylamine); 20 to 30 yrs latency after exposure.

Clinics
Hematuria, irritation.

Pathology
Grading and staging: tumours are:
- graded by the degree of cellular atypia (G0→ G3), and;
- staged: pTIS carcinoma in situ (but high grade), and pTa papillary carcinoma, both mucosally confined; pT1 lamina propria invasive; pT2 infiltrates the superficial muscle, and pT3a, the deep muscle; pT3b invasion into perivesical fat; pT4 extends into neighbouring structures and organs.

Treatment
Resection (more or less extensive: electrofulguration → cystectomy); chemo and/or radiotherapy, BCG-therapy.

Evolution
Recurrence is highly frequent.

Prognosis
According to the stage and the grade; pTa is of good prognosis (> 90% are cured); prognosis is uncertain in pT1 and G2 tumours, where cytogenetic findings may be relevant prognostic indicators. 20% survival at 1 yr (stable at 3 yrs) is found in T4 cases; however, identification of individual patient’s prognosis is often difficult, although of major concern for treatment decision and for follow up.
Cytogenetics

Cytogenetics, morphological
Highly complex and diverse, but non-random.
-9: monosomy 9 is frequent (about 50% of cases, and can be the only anomaly; found also in early stages; not associated with tumour progression; loss of heterozygocity (LOH); critical deletion segments are in 9p21 and somewhere in 9q; gessolin could be implicated.

-11 or del(11p): are frequent; associated with high stages and tumour progression.

del(17p) and LOH at 17p: also frequent; mainly found in pT2 to pT4; also found in a subset of pTIS, which might be a relevant indicator for these tumours with variable often poor prognostic; the deletion involve P53.

del(13q) and Rb loss are correlated with the stage.

+7: often found, but the same occurs in a number of cancers of various origin; may have no pertinence, inasmuch as +7 has also been found in normal (i.e. non tumoural) cells!

Mar, aneuploidy, polyploidy, complex karyotypes: are bad prognostic features.

del(3p), del(5q) and i(5p), del(6q), del(8p), del(14q) and del(18q) are also consisantly found; these LOH point to probable tumour suppression genes, which could be implicated in tumour progression.

Cytogenetics, molecular
Interphase cytogenetics using whole chromosome paints/comparative genomic hybridization (CGH) should prove useful tools; flow cytometry for DNA index measurement has often been used, but appears to be a 'blind' method.

Genes involved and Proteins

Note: as the process is multistep, genes involved in transitional cell carcinoma of the bladder should be numerous; most are still unknown; some are quoted above.

References


This article should be referenced as such:
Naevoid basal cell carcinoma syndrome (NBCS)

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: September 1997

Online version is available at: http://AtlasGeneticsOncology.org/Kprones/NBC10005.html

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Identity

Other names: Gorlin syndrome; Gorlin-Goltz syndrome; Multiple basal cell nevi, odontogenic keratocysts, skeletal anomalies; Fifth phacomatosis; Hydrocephalus, costovertebral dysplasia, sprengel anomaly.

Inheritance: autosomal dominant with complete penetrance, but variable expressivity; 40% are de novo mutations; frequency is about 2/10^5 newborns.

Clinics

NBCS is a hamartoneoplastic syndrome; it is also a chromosome instability syndrome; hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; they are heritable malformations that have a potential towards neoplasia.

Phenotype and clinics

Multiple basal cell carcinomas, appearing as early as 15 yrs;
Jaw keratocysts;
Dyskeratotic palmar/plantar pits;
Skeletal malformations (of ribs, spina bifida occulta...);
Soft tissue calcifications (falx cerebri, ovarian fibroma, diaphragma sellae...);
Facial dysmorphia.

Neoplastic risk

Mainly multiple basal cell carcinomas;
Other proliferations (see below) in 60% of patients;
Other malignancies: medulloblastoma, ovarian fibrosarcoma;
Benign proliferations: ovarian fibroma, menigioma, rhabdomyoma, cardiac fibroma.

Treatment

Tumour exereses.

Evolution

Extensive number of basal cell carcinomas.

Prognosis

According to the tumours (basal cell carcinomas are not life threatening, but may be devastating).

Cytogenetics

Inborn condition

Spontaneous and induced chromosome instability.
Delay in the cell cycle.
NBCS is therefore a chromosome instability syndrome.

Cancer cytogenetics

Poorly documented.

Genes involved and Proteins

Complementation groups

None so far.

PTCH

Location: in 9q22.3 (between FACC and XPAC!!)

Protein

Description: glycoprotein with transmembrane domains, extra cellular loops and intracellular domains.

Localisation: transmembrane protein.

Function: part of a signalling pathway; probable cell to cell adhesion role; may have a repressive activity on cell proliferation; as NBCS syndrome is a chromosome instability syndrome, this protein may have a role in DNA maintenance, repair and/or replication.

Mutations

Germinai: most germ-line mutations in NBCS patients lead to protein truncation, which suggests that developmental anomalies seen in NBCS may be due to haplo-insufficiency; no obvious genotype-phenotype correlations.
**Somatic:** mutation and allele loss events in basal cell carcinoma, in NBCS and in sporadic basal cell carcinoma are, so far, in accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

### References


*This article should be referenced as such:* 
Neurofibromatosis type 1 (NF1)

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

Published in Atlas Database: September 1997

Online version is available at: http://AtlasGeneticsOncology.org/Kprones/NF1ID10006.html

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Identity

Other names: Von Recklinghausen neurofibromatosis; Peripheral neurofibromatosis

Inheritance: autosomal dominant with almost complete penetrance; frequency is 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 a hamartoneoplastic syndrome; hamartomas are localized tissue proliferations with faulty differentiation and mixture of component tissues; they are inheritable malformations that have a potential towards neoplasia.

The embryonic origin of dysgenetic tissues involved in NF1 is ectoblastic.

Phenotype and clinics

Diagnosis is made on the ground of at least 2 of the following:
- Café-au-lait spots (6 or more, over 0.5 cm of diameter (in pre-puberty));
- 2 or more neurofibromas or 1 plexiform neurofibromas (mainly cutaneous);
- 2 or more Lisch nodules (melanocytic hamartomas of the iris);
- Freckling in the axillary/inguinal region (Crowe's sign);
- 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 NF1 patients experience a malignant neoplasm

Neurofibromas, especially the plexiform variety; polyclonal (benign) proliferation; may be present at birth or appear later, may be a few or thousands, small or enormous, occur in the skin and in various tissues and organs; neurofibromas localized to the spine are extremely difficult to manage.

Neurofibrosarcomatous transformation (malignant) of these in 5-10 %.

Schwannomas (optic nerve, see above), meningiomas, astrocytomas, ependymomas.

Childhood MDS (myelodysplasia) and ANLL, often with monosomy 7 (monosomy 7 syndrome, 'juvenile myelomonocytic leukaemia'): risk, increased by X 200 to 500, is still low, as childhood MDS is rare; M > F; 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.

Cytogenetics

Inborn condition

No special feature.

Cancer cytogenetics

According to the cancer type in most cases.

Myelodysplasia and ANLL: monosomy 7.
Genes involved and Proteins

NF1
Location: 17q11.2
Protein
Description: the protein has been called neurofibromin; GTPase activating protein; tumour suppressor.
Mutations
Germinal: nucleotide substitutions, small deletions or insertions on one allele.
Somatic: the second allele remains normal in the benign tumours and is often lost in the malignant tumours.

To be noted
Beside neurofibromatosis 1 and 2 (NF2), other types of neurofibromatoses are numbered and named 3 to 9, some of them being known to involve other loci.

References

This article should be referenced as such:
Neurofibromatosis type 2 (NF2)
Jean-Loup Huret

Cancer Prone Disease Section
Mini Review

Identity

Other names: Central neurofibromatosis; Bilateral acoustic neurofibromatosis; Bilateral acoustic neurinoma; Bilateral acoustic schwannomas

Inheritance: autosomal dominant with almost complete penetrance; frequency is 3/10^5 newborns; neomutation represent 50% of cases; variable expressivity from mild disease through life (Gardner type) to severe condition at young age (Wishart type: with more than 3 tumours).

Clinics

NF2 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.

Phenotype and clinics

Bilateral vestibular (8th cranial pair) schwannomas; other central or peripheral nerve schwannomas; meningiomas; ependymomas.
Hearing loss (average age 20 yrs), tinnitus, imbalance, headache, cataract in 50%, facial paralysis.
Café-au-lait spots and cutaneous and peripheral neurofibromas may be present, but far less extensively than in neurofibromatosis type 1.

Neoplastic risk

NF2 cases represent about 5% of schwannomas and meningiomas (i.e. risk increased by 2000), appearing at the age of 20, while they are found in the general population at the age of 50 and over.

Prognosis

These tumours are usually benign, but their location within the central nervous system gives them a grave prognosis; patients with the Wishart severe form usually do not survive past 50 yrs.

Cytogenetics

Inborn condition
Normal.

Cancer cytogenetics
Chromosome 22 loss is very frequent both in sporadic and in NF2 schwannomas and meningiomas.

Genes involved and Proteins

SCH

Location: 22q12.1-12.2 junction, (incidentally not far from EWS (Ewing tumour))
DNA/RNA
Description: 16 exons; 120 kb.
Transcription: alternate splicing after exon 15.
Protein
Protein has been called schwannomin or SCH.
Description: 590 or 595 amino acids; 66 kDa; domains: NH2 -- membrane binding -- a helix binding to actin of the cytoskeleton -- COOH.
Expression: in lung, kidney, ovary, breast, placenta, neuroblasts.
Function: membrane-cytoskeleton anchor (as APC also appears to be); has characteristics of a tumour suppressor, as has been found in sporadic as well as NF2 induced schwannomas and meningiomas (accordingly to the Rb model).
Homology ezrin, radixin, moesin, members of the erythrocytes band 4.1 family, especially so in the N-term.
Mutations
Germinal: (inborn condition of NF2 patients): protein truncations due to various frameshift deletions or insertions or nonsense mutations; splice-site or missense mutations are also found; phenotype-genotype correlations are observed (i.e. that severe
Neurofibromatosis type 2 (NF2) Huret JL

Atlas Genet Cytogenet Oncol Haematol. 1997; 1(1)

phenotypes are found in cases with protein truncations rather than those with amino acid substitution).  
**Somatic:** tumourigenesis in NF2 patients.

References


**This article should be referenced as such:**

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