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 correspondance

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Multiple myeloma
Jean-Loup Huret

$t(1;7)(p32;q34); t(1;14)(p32;q11); 1p32 rearrangements$
Jean-Loup Huret

$t(3;13)(q27;q14)$
Jean-Loup Huret, Jean-Luc Laï

$t(3;21)(q26;q22)$
Jean-Loup Huret, François Desangles

$t(4;12)(q11-q21;p13)$
Jean-Loup Huret, Marina Lafage-Pochitaloff

$t(5;12)(q33;p13)$
Jean-Loup Huret

$t(6;9)(p23;q34)$
Jean-Loup Huret

$t(10;11)(p13;q21)$
Jean-Loup Huret

$t(11;14)(q13;q32)$ in multiple myeloma
Jean-Loup Huret, Jean-Luc Laï
# CALM (clathrin assembly lymphoid myeloid leukemia gene)

**Jean-Loup Huret**

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

Published in Atlas Database: January 1998

Online version is available at: http://AtlasGeneticsOncology.org/Genes/CALM.html

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## Identity

<table>
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<th>Location: 11q14-21</th>
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Probe(s) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

## DNA/RNA

### Transcription

Major mRNA: 4 kb; other: 3 and 9 kb.

## Protein

### Description

652 amino acids.

### Expression

Wide.

### Function

Role in the integration of signals from different pathways (clathrin, phosphoinositols, receptor-mediated endocytosis).

### Homology

With ap-3, a clathrin assembly protein (mouse).

## Implicated in

\[
\text{t}(10;11)(p13;q14-21) \rightarrow \text{CALM/AF10 and/or AF10/CALM}
\]

### Disease

Yet to be well delineated; T-cell ALL.

### Prognosis

Uncertain (median survival 2 yrs?).

### Cytogenetics

May well be confused with the \( \text{t}(10;11)(p12;q23) \), where MLL on 11q23 is involved, instead of CALM.

### Hybrid/Mutated Gene

5' CALM - 3' AF10 and 5' AF10 - 3' CALM.

### Abnormal Protein

Both CALM-AF10 and the reciprocal AF10-CALM are expressed.

## References


Kobayashi H, Hosoda F, Maseki N, Sakurai M, Imashuku S, Ohki M, Kaneko Y. Hematologic malignancies with the \( \text{t}(10;11)(p13;q21) \) have the same molecular event and a variety of morphologic or immunologic phenotypes. Genes Chromosomes Cancer 1997 Nov;20(3):253-9.

*This article should be referenced as such:*

CAN (CAN protein, putative oncogene)

Jean-Loup Huret

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

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Identity

Other names: CAIN; NUP214 (nuclear pore complex protein 214 kDa); nucleoporin

Location: 9q34.3

Local order: more telomeric than ABL1; less than TAN1.

DNA/RNA

Description

Spans on a 130 kb and more genomic segment.

Transcription

7.5 kb mRNA.

Protein

Description

2090 amino acids; 214 kDa; dimerization domains (2 leucine zippers) and FG repeats; forms homodimers.

Expression

Thymus, bone marrow, spleen, kidney, testis, brain; apparently not in other tissues.

Localisation

Nuclear membrane localisation.

Function

Nucleoporin: associated with the nuclear pore complex; role in nucleocytoplasmic transport processes and cell cycle progression.

Homology

C-term part of CAN has homologies with proteins of the nucleoporin family.

Implicated in

\( t(6;9)(p23;q34)/\text{ANLL or MDS} \rightarrow \text{DEK/CAN} \)

Disease

M2, M4 ANLL or MDS.

Prognosis

Remission difficult to obtain.

Cytogenetics

This chromosome anomaly may be over looked.

Hybrid/Mutated Gene

5’ DEK - 3’ CAN; chromosome 6 breakpoint clusters in a single intron.

Abnormal Protein

Head to tail DEK/CAN fusion protein (the alternative SET/CAN is exceptional); almost the entire DEK protein is fused to the C-terminal two-thirds of the CAN protein; nuclear localization.

\( t(6;9)(p23;q34)/\text{AUL} \rightarrow \text{SET/CAN} \)

(exceptional)

References


This article should be referenced as such:

DDX10 (DEAD (Asp-Glu-Ala-Asp) box polypeptide 10)

Jean-Loup Huret

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

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Identity

Other names: HRH-J8
Location: 11q22
Local order: telomeric to ATM.

DNA/RNA

Description
At least 12 exons; spans more than a 200 kb region.

Transcription
Alternative splicing; 3.2 and 5.0 kb mRNA.

Protein

Description
Contains 2 nuclear localization signals (NLS), a DEAD box (DEAD for: ASP-GLU_ALA-ASP).

Expression
Wide.

Localisation
Nucleolus (probable).

Function
Putative ATP-dependent DEAD box RNA helicase; possible role in ribosome assembly through rRNA processing.

Homology
SPB4 and DRS1 (yeast).
Implicated in

*inv(11)(p15q22)/MDS or ANLL → NUP98/DDX10*

**Disease**
Therapy related MDS and ANLL; de novo ANLL.

**Hybrid/Mutated Gene**
5’ NUP98 - 3’ DDX10.

**Abnormal Protein**
Fuses the GLFG repeat domains of NUP98 to the charged amino acids domain of DDX11.

---

**References**


This article should be referenced as such:

DEK (DEK oncogene)

Jean-Loup Huret

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

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Identity

Location: 6p23

DEK (6p23) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact rocchi@biologia.uniba.it.

DNA/RNA

Description
Spans on a 40 kb genomic segment.

Transcription
2.7 kb mRNA; coding sequence: 1.1 kb.

Protein

Description
375 amino acids; 43 kDa; contains numerous acidic domains (Asp/Glu rich) and a nuclear localisation signal.

Expression
Wide.

Localisation
Potentially nuclear.

Function
Site specific DNA binding protein involved in transcriptional regulation and signal transduction.

Implicated in

t(6;9)(p23;q34)/ANLL or MDS

→DEK/CAN

Disease
M2, M4 ANLL or MDS.

Prognosis
Remission difficult to obtain.

Cytogenetics
This chromosome anomaly may be over looked.

Hybrid/Mutated Gene
5' DEK - 3' CAN; chromosome 6 breakpoint clusters in a single intron.

Abnormal Protein
Head to tail DEK/CAN fusion protein (the alternative SET/CAN is exceptional); almost the entire DEK protein fused to the C-terminal two-thirds of the CAN protein; nuclear localization.

References


This article should be referenced as such:

HOXA9 (homeobox A9)

Jean-Loup Huret

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

Published in Atlas Database: January 1998


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Identity

Other names: HOX1G (homeobox-1G)
Location: 7p15

Protein

Description
129 amino acids; DNA binding domain (homeobox) in C-term.

Localisation
Nuclear.

Function
Sequence specific transcription factor; role during embryonic development (patterning); HOX genes are also expressed in adult tissues, including blood cells; probable role in blood cell differentiation.

Homology
With class 1 homeodomain proteins.

Implicated in

\[ t(7;11)(p15;p15)/ANLL \rightarrow NUP98/HOXA9 \]

Disease
M2-M4 ANLL mostly; occasionally: CML-like cases.

Prognosis
Mean survival: 15 mths.

Cytogenetics
Sole anomaly most often.

Hybrid/Mutated Gene
5' NUP98 - 3' HOXA9.

Abnormal Protein
Fuses the GLFG repeat domains of NUP98 to the HOXA9 homeobox.

References


This article should be referenced as such:

NUP98 (nucleoporin 98 kDa)

Jean-Loup Huret

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

Published in Atlas Database: January 1998

Online version is available at: http://AtlasGeneticsOncology.org/Genes/NUP98.html

DOI: 10.4267/2042/32093

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Identity

Location: 11p15

DNA/RNA

Transcription

3.6, 6.5, 7.0 kb mRNA.

Protein

Description

920 amino acids; 97 kDa; contains repeated motifs (GLFG and FG) in N-term and a RNA binding motif in C-term.

Expression

Wide.

Localisation

Nuclear membrane localisation.

Function

Nucleoporin: associated with the nuclear pore complex; role in nucleocytoplasmic transport processes.

Homology

Member of the GLFG nucleoporins.

Implicated in

\[ t(7;11)(p15;p15)/ANLL \rightarrow NUP98/HOXA9 \]

Disease

M2-M4 ANLL mostly; occasionally: CML-like cases.

Prognosis

Mean survival: 15 mths.

Cytogenetics

Sole anomaly most often.

Hybrid/Mutated Gene

5’ NUP98 - 3’ HOXA9.

Abnormal Protein

Fuses the GLFG repeat domains of NUP98 to the HOXA9 homeobox.

\[ \text{inv}(11)(p15q22)/\text{MDS or ANLL} \rightarrow \text{NUP98/DDX10} \]

Disease

Therapy related MDS and ANLL; de novo ANLL.

Hybrid/Mutated Gene

5’ NUP98 - 3’ DDX10.

Abnormal Protein

Fuses the GLFG repeat domains of NUP98 to the acidic domain of DDX10.

References


This article should be referenced as such:

BLM (Bloom)
Jean-Loup Huret

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


DOI: 10.4267/2042/32095

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Identity
Location: 15q26.1

DNA/RNA

Transcription
4.4 kb mRNA.

Protein

Description
1417 amino acids; ATP binding in amino acid 689-696; DEAH box in 795-798; two putative nuclear localization signals in the C-term in 1334-1349.

Localisation
Nuclear.

Function
DNA helicase; probable role in DNA replication and repair; possibly also in transcription regulation.

Homology
Homologous to RecQ helicases, a subfamily of DExH box-containing DNA and RNA helicases; in particular, similarity with the gene mutated in Werner syndrome, WRN, another member of the RecQ family; Werner syndrome is another cancer-prone disease.

Mutations

Germinal
The mutated BLM protein is retained in the cytoplasm or both in the cytoplasm and the nucleus, while the normal protein is nuclear.

Implicated in

Bloom syndrome

Disease
Bloom syndrome is a chromosome instability syndrome/cancer prone disease (at risk of numerous, early occurring cancers of various types).

Prognosis
1/3 of patients are dead at mean age 24 yrs, and the mean age of the 2/3 remaining alive patients is 22 yrs.

Cytogenetics
Chromatid/chromosome breaks; triradial and quadriradial figures, highly elevated spontaneous sister chromatid exchange rate.

References


This article should be referenced as such:
TRIP11 (thyroid hormone receptor interactor 11)

Jean-Loup Huret

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

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Identity

Location: 14q32

DNA/RNA

Transcription

Major transcripts: 7, 9 and 10.5 kb; coding sequence: 2.2 kb.

Protein

Description

729 amino acids; contains a N-term leucine zipper and a C-term putative thyroid hormone receptor interacting domain.

Expression

Is wide; high expression in heart, muscle, pancreas; found expressed in hematopoietic cell lines.

Function

May be a transcriptional factor.

Implicated in

t(5;14)(q33;q32)/ANLL → CEV14/PDGFRb

Disease

Poorly known: 1 case of ANLL.

Cytogenetics

Found as an additional anomaly.

Hybrid/Mutated Gene

5’ CEV14 - 3’ PDGFRb.

Abnormal Protein

Leucine zipper from CEV14 fused to the transmembrane domain and the Tyr kinase domain of PDGFRb.

References


This article should be referenced as such:

FACC (Fanconi anaemia complementation group C)

Jean-Loup Huret

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

Published in Atlas Database: February 1998

Online version is available at: http://AtlasGeneticsOncology.org/Genes/FACC101.html

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Identity

Other names: FAC
Location: in 9q22.3
Local order: next to PTCH and XPAC.

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

DNA/RNA

Description
14 exons; spans 80 kb.

Transcription
mRNA of 2.3, 3.2, and 4.6 kb (variable 3’ untranslated region, alternative splicing, exon skipping).

Protein

Description
558 amino acids; 63 kDa; alpha helical structure in C-term.

Expression
Wide, in particular in the bones.

Localisation
Cytoplasmic at any cell-cycle stage.

Function

Peak expression during the G2/M transition; binds to cdc2 (mitotic cyclin-dependent kinase); probably involved in basic aspect(s) of the cell protection against DNA damages: role in the cell cycle regulation and/or in DNA repair and/or in the prevention of cellular apoptosis; binds to FAA, the protein encoded by FA1 (Fanconi anaemia complementation group A), the dimer being found in the cytoplasm and the nucleus.

Homology

No known homology.

Mutations

Germinal
Mainly nucleotide substitutions, dispersed along the coding sequence.

Implicated in

Fanconi anaemia; FACC is implicated in the FA complementation group C

Disease
Fanconi anaemia is a chromosome instability syndrome/cancer prone disease (at risk of leukaemia).

Prognosis
Poor; mean survival is 16 years: patients die of bone marrow failure (infections, haemorrhages), leukaemia, or androgen therapy related liver tumours.

Cytogenetics
Spontaneous, chromatid/chromosome breaks; increased rate of breaks compared to control, when induced by breaking agent.

References


This article should be referenced as such:
FGFR3 (fibroblast growth factor receptor 3)

Jacky Bonaventure

Unité INSERM 393, Hopital Necker-Enfants Malades, 149 rue de Sèvres 75743, Paris Cedex 15, France

Published in Atlas Database: February 1998

Online version is available at: http://AtlasGeneticsOncology.org/Genes/FGFR99.html
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Identity

Location: 4p16.3
Local order: centromere - IT 15 - FGFR 3 - IDUA - MYL 5 - ZNF 141 - telomere.

DNA/RNA

c-FGFR3 (4p16.3) in normal cells; PAC 1054L13 (above) and PAC 1174P18 (below) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

Description

16.5 kb; 19 exons; exon 1 unknown in human.

Transcription

4.0 kb mRNA; large 3’ untranslated region (1.4 kb); alternative splicing of exons 7 and 8 gives rise to two isoforms IIIb and IIIc.

Protein

Description

806 amino acids; 115 kDa; tyrosine kinase receptor; contains three major domains: an extracellular domain with 3 Ig-like loops, a highly hydrophobic transmembrane domain (22 amino acids) and an intracellular domain with tyrosine kinase activity.

Expression

Mostly in brain, cartilage, liver, inner ear, kidney.

Localisation

Plasma membrane.

Function

FGF receptor with tyrosine kinase activity; binding of ligand (FGF) induces receptor dimerization, autophosphorylation and signal transduction.

Homology

With other FGFR (1, 2 and 4); Cek 2 in chicken.

Diagram:

mutations in FGFR3 in the following squeueletal dysplasia:
TD I and II: thanatophoric dysplasia
ACH: achondroplasia
HCH: hypochondroplasia

FGFR3

Sign Ig-like acid Ig-like Ig-like trans-mb Tyr-k Tyr-k

Sign: signal sequence
acid: acidic amine acid rich domain
trans-mb: transmembrane
Tyr-k: Tyr kinase
**Implicated in**

\[ t(4;14)(p16.3;q32.3)/\text{multiple myeloma} \rightarrow \text{FGFR3/IgH} \]

**Disease**
Plasma cell leukaemia and multiple myeloma.

**Prognosis**
Unknown: found in 11 cases, but with no data on clinics.

**Abnormal Protein**
No fusion protein, but promoter exchange between both partner genes.

**Oncogenesis**
Overexpression and activation of FGFR 3 provides an oncogenic signal.

**Skeletal dysplasia (inborn diseases)**

**Disease**
Hypochondroplasia, achondroplasia, thanatophoric dwarfism (TD I and II), Crouzon syndrome with acanthosis nigricans and coronal craniosynostosis; endochondral and membranous ossification defects are caused by recurrent missense mutations.

**References**

This article should be referenced as such:
JAK2 (janus kinase 2)

Jean-Loup Huret

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

Published in Atlas Database: February 1998

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Identity

Location: 9p24

DNA/RNA

Description
24 exons spanning 140 kb; 4.2 kb cDNA.

Protein

Description
1132 amino acids.

Expression
Wide.

Localisation
Possibly membrane associated.

Function
Tyrosine kinase; associates with the intracellular domains of cytokine receptors; signal transduction.

Homology
>90% identical to the mouse and the rat JAK2 homologs; belongs to the janus kinase subfamily (JAK1, JAK3, TYK2).

Implicated in

`t(9;12)(p24;p13)/acute leukaemias → JAK2/ETV6`

Prognosis
Unknown.

Hybrid/Mutated Gene
5’ ETV6 - 3’ JAK2.

Abnormal Protein
N-term- HLH from ETV6 fused to the tyrosine Kinase c-term domains of JAK2.

Oncogenesis
It may be speculated that the HLH domain of ETV6 provides a dimerization interface to the kinase domain of JAK2, which activates JAK2.

References


This article should be referenced as such:

**Identity**

**Other names:** TTF (translocation three four); ARHH  
**Location:** 4p13

![RHOH (4p13) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact rocchi@biologia.uniba.it.]

**DNA/RNA**

**Description**  
Spans on a 35 kb genomic fragment; two exons separated by a large intron; small GTPase encoding gene.

**Transcription**  
2.2 kb mRNA; coding sequence: 575 bp, located in the second exon.

**Protein**

**Description**  
191 amino acids; 21 kDa; contains a GTP binding motif, a GTPase activity site, and a membrane localisation signal (CAAX box) in the very C-term.

**Expression**  
Restricted to the haemopoietic tissues.

**Localisation**  
Plasmic membrane.

**Function**  
Small GTPase of the Rho subfamily; involved in signal transduction and cytoskeletal reorganization.

**Homology**  
With all GTPases of the Ras superfamily.

**Implicated in**

**t(3;4)(q27;p13)/NHL → BCL6/RHOH**

**Disease**  
Follicular NHL.

**Cytogenetics**  
Observed as a secondary anomaly.

**Hybrid/Mutated Gene**  
5' RHOH - 3' BCL6 and 5' BCL6 - 3' RHOH, are leading to two fusion transcripts.

**Abnormal Protein**  
No fusion protein, but promoter exchange between both partner genes.

**t(4;14)(p13;q32)/multiple myeloma → RHOH/?**

**Disease**  
Multiple myeloma.

**Prognosis**  
Still unknown: only 1 available case.

**Cytogenetics**  
Observed as a unique anomaly.

**Hybrid/Mutated Gene**  
Not yet known (under study).

**Abnormal Protein**  
No fusion protein.
References


This article should be referenced as such:
Myelofibrosis with Myeloid Metaplasia (MMM)
Idiopathic myelofibrosis
Agnogenic myeloid metaplasia

Jean-Loup Huret

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

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**Clinics and pathology**

**Disease**
Chronic myeloproliferative syndrome.

**Phenotype / cell stem origin**
Pluripotent stem cell is involved.

**Epidemiology**
Annual incidence: 2/10^6; slightly more frequent in males; age is usually over 50 yrs.

**Clinics**
Asymptomatic for a long time, revealed by symptoms related to the splenomegaly, or by anaemia/asthenia; splenomegaly is the major sign; hepatomegaly in 50%; blood data: anisocytosis, poikilocytosis (as tears drops, are characteristic); anaemia is frequent; hyperleucocytosis in 60%; thrombocytosis may be present; erythromyelemia.

**Cytology**
Bone marrow: fibrosis is major (fibrosis is a secondary event in this disease), while there is extramedullary hematopoiesis (myeloid metaplasia) in the spleen, the liver, and anywhere (e.g. skin).

**Prognosis**
Evolution: this is a chronic disease, with a proliferative stage followed by a pancytopenic stage; pancytopenia and portal hypertension are the major causes of death in this disease; evolution towards ANLL is found in 15-20% of cases; prognosis: is highly variable; survival is frequently over 10-15 yrs, but death occurs within a year in some cases; cases with pancytopenia directly at diagnosis bear a worse prognosis; probable prognostic factors are: the presence of an abnormal karyotype and a low haemoglobin level, possibly a low platelets count and a high WBC, a higher age, and hepatomegaly.

**Cytogenetics**

**Cytogenetics, morphological**
An abnormal karyotype is found in 40% of cases at diagnosis: der(1), in particular partial trisomy 1, del(5q) or -5, -7, +8, +9, del(13q), del(20q) are seen solely or simultaneously in 5-10% of cases with chromosome anomalies, and other (various) anomalies in 40%.

**Genes involved and Proteins**

Note: genes involved are unknown.

**To be noted**

'Acute myelofibrosis' is a megakaryoblastic leukaemia (M7 ANLL) with prominent fibrosis.

**References**


This article should be referenced as such:
Multiple myeloma
Jean-Loup Huret

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

Published in Atlas Database: January 1998

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Disease

Multiple myeloma (MM) is a malignant plasma cell proliferation.

Phenotype / cell stem origin
Phenotype of mature terminally differentiated B-cell, but also with CD56 expression, which is not found in normal plasma cells; CD38+ CD40+.

Epidemiology
Multiple myeloma's annual incidence: 30/10^6; i.e. around 1% of malignancies in adults and 10% of haematologic malignancies; mean age: 62 yrs.

Clinics
Patients may be asymptomatic at the time of diagnosis; bone pain; susceptibility to infections; renal failure; neurologic dysfunctions.

Pathology
MM staging: stage I: tumour cell mass < 0.6 X 10^12/m²; Hb> 10 g/dl; serum calcium ¾ 120 mg/l; no bone lesion; low monoclonal Ig rate (IgG < 50 g/l, IgA < 30 g/l, BJ urine < 4 g/day); stage II: fitting neither stage I nor stage II; stage III: tumour cell mass > 1.2 X 10^12/m²; Hb < 8.5 g/dl and/or serum calcium > 120 mg/l and/or advanced lytic bone lesions and/or high monoclonal Ig rate (IgG > 70 g/l, IgA > 50 g/l, BJ urine > 12 g/day).

Treatment
None before onset of symptoms; chemotherapy or BMT afterwards.

Prognosis
Evolution: multiple myeloma can evolve towards plasma cell leukaemia, where plasma cell count is greater than 2000/mm³; survival is highly variable (median is around 3 yrs); prognosis is according to the staging and other parameters (such as age, serum albumin, b2 microglobulin, C-reactive protein, and plasma cell labeling index); the karyotype is emerging as an important prognostic factor: median survival in case of a normal karyotype could be 4 yrs vs 1 yr in case of -13/del(13q) and/or 11q rearrangements (the chromosome anomalies with the worst prognostic impact).

Cytogenetics

Cytogenetics, morphological
Cytogenetic information is limited, as the malignant cells have a low spontaneous proliferative activity; abnormal karyotypes are found in 30-50% of cases, more often in advanced stages than in newly diagnosed patients (is this because chromosome abnormalities are secondary events, or because malignant cells have an increased proliferative activity in advanced stages: see below);

Karyotypes are complex; hyperploidy is found in 2/3 of cases; karyotypes may evolve from normal to abnormal during course of the disease; monosomy 13 or del(13q) is found in about 40% of MM cases with an abnormal karyotype; structural (and variable) anomalies of chromosome 1 are found in 30-40% of cases; 14q rearrangements: 25% of cases; 11q abnormalities 20 %; t(11;14) representing 10%; 6q anomalies represent 15% of cases.

Cytogenetics, molecular
FISH is indicated, as metaphases are arduous to obtain in such a disease implicating mature cells, and tend to show that most cases bear chromosome anomalies, irrespective of the disease staging.

Genes involved and Proteins

C-MYC
Location: 8q24

Note: Overexpression (mainly without rearrangement or amplification) correlated with increased tumour cell burden. RAS mutations (found in 20% of cases) and P53 mutations are associated with advanced disease.
**RB1**

*Location:* 13q14  
*Note:* RB1 is deleted in more than 1/3 of cases.

**BCL1**

*Location:* 11q13  
*Note:* BCL1 is involved in t(11;14) cases.

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**References**


This article should be referenced as such:

t(1;7)(p32;q34)
t(1;14)(p32;q11)

1p32 rearrangements

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

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Identity

Note: the two chromosome anomalies are variants of each other, and they share identical features.

![Image of chromosome anomalies]

Disease

T- cell ALL.

Epidemiology

Rare findings; t(1;14) is found in approximately 3% of T-ALL; t(1;7) is rarer (status 3: < 5 cases); however, TAL1 rearrangements, altogether (being mostly submicroscopic deletions without visible 1p32 involvement), occurs in 15-25% of T-ALL; male predominance (as is classical in T-cell ALL).

Clinics

Organomegaly; high WBC (median 200 X 10^9/l).
Cytogenetics

Additional anomalies

$t(1;14)$ is found solely in about half cases, and accompanied by del(6q) in nearly half cases as well.

Genes involved and Proteins

**TAL1**

*Location:* $1p32$

*DNA / RNA*

Complex alternate splicing.

*Protein*

Contains a basic Helix-Loop-Helix (DNA binding) domain; forms heterodimers; transcription factor; role in haematopoietic cell differentiation.

**TRA/D**

*Location:* $14q11$ in the case of a $t(1;14)$.

**TRB**

*Location:* $7q35$ in the case of a $t(1;7)$.

Result of the chromosomal anomaly

**Fusion protein**

*Description*

In most cases (breakpoints between exons 2B and 3 of TAL1), 3' TAL1 joins variable and diversity segments of TCR on der(14); in the few cases where the breakpoint is within exon 6 of TAL1 or 3' from it, constant segments of TCR join TAL1 on der(1).

References


This article should be referenced as such:

Leukaemia Section
Short Communication

\(t(3;13)(q27;q14)\)

Jean-Loup Huret, Jean-Luc Laï

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH); INSERM Unité 524, Institut de Recherche sur le Cancer de Lille, Lille, France (JLL)

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Identity

\(t(3;13)(q27;q14-21), t(14;18)(q32;q21)\) G-banding - Courtesy Jean-Luc Laï.

Clinics and pathology

**Disease**

NHL

**Phenotype / cell stem origin**

Found in various types of NHL (e.g. Burkitt's lymphoma and follicular lymphoma); the translocation is therefore likely to be a secondary event in the course of the disease.

**Epidemiology**

Only 3 cases available to date; all three are adult female patients.

Cytogenetics

**Cytogenetics, morphological**

Found twice (out of three occurrence) as a secondary anomaly: following the well known \(t(8;14)(q24;q32)\) and \(t(14;18)(q32;q21)\).

**Additional anomalies**

del(6q) found in 2 of 3 cases; the karyotype may be complex.
**Genes involved and Proteins**

**BCL6**  
*Location:* 3q27

**L-plastin**  
*Location:* 13q14-21

**References**


*This article should be referenced as such:*  
t(3;21)(q26;q22)

Jean-Loup Huret, François Desangles

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH); Laboratoire de Biologie, Hôpital du Val de Grâce, 75230 Paris, France (FD)

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Identity

Clinics and pathology

Disease
CML-BC of myeloid type (as far as 1% of cases); ANLL and MDS, often therapy related.
Phenotype / cell stem origin
No FAB specificity.

Epidemiology
>1% of ANLL; all ages represented.
Clinics
May be secondary to toxic exposure, as to antitopoisomerase II.
Cytology
Presence of micromegakaryocytes, both in BC-CML and MDS/ANLL cases; low platelet count and dysmyelopoiesis in MDS/ANLL cases.
Prognosis
Poor survival.

**Genes involved and Proteins**

**EVI1**

**Location:** 3q26

**Note:** or EAP (129 amino acids; putative nuclear localization signal) and/or MDS1 (rich in: proline, serine, and acidic residues), both also in 3q26.

**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**

Fusion gene: on the der(3); 5' AML1 - 3' EVI1 (or 5' AML1 - 3' EAP/MDS1).

**Fusion protein**

**Description**

AML1-EVI1: 180 kDa; breakpoint after exon 5 or 6 in AML1, at the very 5' end of EVI1 → translocation protein includes N-term AML1 with the Runt domain and most of the gene EVI1, from the second untranslated exon to C-term, which includes the 2 zinc fingers.

**Oncogenesis**

Chimeric transcription factor with the dual functions of AML1 and EVI1: differentiation block (due to Runt) and stimulation of proliferation (from the zinc fingers).

**References**


This article should be referenced as such:

t(4;12)(q11-q21;p13)

Jean-Loup Huret, Marina Lafage-Pochitaloff

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH); Laboratoire de Cytogénétique Hématologique, Institut Paoli-Calmettes, Marseille, France (MLP)

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Identity

Note: it is likely that breakpoints are heterogeneous, with 2 distinct entities: t(4;12)(q11-12;p13) in ANLL, and t(4;12)(q13-21;p13) in ALL to be delineated.

Clinics and pathology

Disease
ANLL and therapy related AL cases with t(4;12)(q11-12;p13); B-cell ALL cases seem to have a more distal breakpoint in 4q13 or 21.

Phenotype / cell stem origin
ANLL cases: M0, M1, and other subtypes; often CD7+; a stem cell may be involved; ALL cases are CD10+.

Epidemiology
Only 13 available cases: 9 ANLL and 4 ALL; so far, ANLL cases with a proximal breakpoint in 4q11 or 12 are adult cases (43-77 yrs), and ALL cases are children cases (3-14 yrs); balanced sex ratio.

Prognosis
Adult cases: response to therapy is poor and median survival might be a year.

Cytogenetics

Additional anomalies
None in 5/12 cases (all 5 cases are ANLL); del(6q) has recurrently been found in ALL; -7 would be recurrent if only 1 entity exists; the karyotype in ALL cases can be complex.

Genes involved and Proteins

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(5;12)(q33;p13)

Jean-Loup Huret

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

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Identity

Note: this translocation must not be confused with the t(5;12)(q31;p13) found in an ALL cell line with IL3 and ETV6 involvements.

Clinics and pathology

Disease
Myeloid lineage.

Phenotype / cell stem origin
Myeloproliferative/myelodysplastic syndrome (intermediate between CML and CMML) with eosinophilia; appear to be a specific entity.

Epidemiology
Rarely described; mostly in adult male patients (13 of 14 cases herein reviewed).

Clinics
Organomegaly in 9 of 12 cases; blood data: median WBC: 40 X 10^9/l; numerous eosinophils: median 2.8 X 10^9/l, range 0.8-128 X 10^9/l, n=9 (normal range is 0.02-0.45 X 10^9/l), and, at times, of monocytes; no blast cells.

Treatment
Hydroxyurea alone or polychemotherapy have been essayed.

Prognosis
Yet partly undetermined; median survival < 20 mths (n=11).
Cytogenetics

Additional anomalies
+8.

Genes involved and Proteins

**PDGFRB**
Location: 5q33
Protein
PDGFRB is the receptor for PDGF (platelet-derived growth factor-b); membrane protein; belongs to the immunoglobulin superfamily.

**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.

Results of the chromosomal anomaly

**Hybrid gene**

Description
5' ETV6 - 3' PDGFRB.

**Fusion protein**
Description
N-term HLH domain of ETV6 fused to the transmembrane domain and the Tyr kinase domain of PDGFRb in C-term; the reciprocal transcript is not expressed.

References


This article should be referenced as such:
t(6;9)(p23;q34)

Jean-Loup Huret

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

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Identity

Phenotype / cell stem origin
M2, M4 ANLL, often preceded by MDS; M1 ANLL or RAEB at times; May be secondary to toxic exposure; A primitive myeloid progenitor is likely to be involved.

Epidemiology
1% of ANLL; Found at any age, but median age (25-30 yrs) is less than usual in ANLL; Rare in the elderly; Sex ratio: 1M/1F; Blood data: marked basophilia (> 1% of nucleated cells) in one third to half of the patients.

Cytology
TdT +; Auer rods.

Prognosis
Remission difficult to obtain; CR in only half cases; median survival around 1 yr.

Cytogenetics

Cytogenetics, morphological
May be over looked.

Additional anomalies
Most often none (80%); recurrent, although rare, additional anomalies are: +8, +13, +21.

Variants
Three way complex t(6;9;Var) exist.

Genes involved and Proteins

DEK
Location: 6p23
Protein
Contains acidic domains and a nuclear localisation signal; DNA binding protein; transcriptional regulation and signal transduction.
The translocation t(6;9)(p23;q34) results in the formation of a chimeric fusion gene: DEK (6q23) and CAN (9q34). CAN is a putative oncogene which may be activated by fusion of its 3’ end to other genes than DEK. One such recently reported gene is called SET and leads to expression of a SET/CAN fusion RNA. The t(6;9)(p21-22;q34) may be seen in either AML M2 or less frequently in M4 or MDS and acute myelofibrosis often in association with excess basophils. The t(6;9) is reported mostly in young adults. The prognosis of patients carrying the t(6;9) is unfavorable - Courtesy Georges Flandrin, CD-ROM AML/MDS G.Flandrin/ICG. TRIBVN.

**CAN**

**Location:** 9q34

**Protein**
Contains dimerization domains → forms homodimers; nuclear membrane localisation; associated with the nuclear pore complex.

**Results of the chromosomal anomaly**

**Hybrid gene**

**Description**
5’ DEK - 3’ CAN on der(6); Head to tail DEK/CAN fusion gene (SET/CAN exceptional); breakpoint clusters in a single intron of 8 kb (ICB9: ‘intron containing breakpoint 9’) in CAN, and in a single intron (of 12 kb) as well (ICB6) in DEK.

**Transcript**
5.5 kb RNA; no CAN-DEK reciprocal transcript on chromosome 9.

**Detection protocol**
RNA-PCR.

**Fusion protein**

**Description**
165 kDa; N-term with almost the entire DEK protein fused to the C-terminal two-thirds of the CAN protein.

**Expression localisation**
Nuclear localisation.

**References**


Soekarman D, von Lindern M, van der Plas DC, Selleri L, Bartram CR, Martiat P, Culligan D, Padua RA, Hasper-Voogt...


This article should be referenced as such:
t(10;11)(p13;q21)

Jean-Loup Huret

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

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Identity

Note: the description of this rare entity is arduous, since cases without molecular studies can be confused with cases of t(10;11)(p12;q23).

t(10;11)(p13;q21) R-banding (left) and Fish studies with MLL probe showing a signal on the normal 11 and one on the der(10)(right) and with chromosome 11 paint - Courtesy Pascale Cornillet-Lefebvre and Stéphanie Struski.

Clinics and pathology

Disease

A mainly T-cell ALL; at times ANLL and/or ANLL with T-cell markers, or B-cell ALL.

Phenotype / cell stem origin

A myelomonocytic/T-cell common progenitor may be involved; FAB: L1/L2.

Epidemiology

< 1% of ALL; about 5% of T-ALL; sex ratio: 9M/5F (from 14 cases herein reviewed).

Clinics

Organomegaly; no CNS involvement; blood data: high WBC (range 20-170 X 10^9/l).

Prognosis

Median survival: 22 mths in this review; range: 0-33+ mths, n=11 (but we are to be cautious: cases ascertained by molecular studies are needed before true prognostic ascertainment).

Cytogenetics

Cytogenetics, molecular

Investigations are required.

Additional anomalies

Most often (11/15 cases) present; del(5q), +8, and +19 already recurrent.

Genes involved and Proteins

AF10

Location: 10p12

DNA / RNA

5’ telomeric → 3’ centromeric orientation.
Protein
Contains 3 Zn fingers and a leucine zipper; nuclear localisation; transcription factor.

**CALM**

*Location:* 11q14-21

**Protein**
Role in the integration of different signals.

### Results of the chromosomal anomaly

**Hybrid gene**

**Transcript**
Both 5’ CALM - 3’ AF10 and 5’ AF10 - 3’ CALM are expressed.

**Fusion protein**

**Description**

1. A 1595 amino acids protein with N-term and most of CALM (except the last 4 amino acids!) fused to most of AF10 from amino acid 81 (excluding the N-term zinc finger of AF10) C-term.

2. A small 84 amino acids protein with N-term zinc finger from AF10 fused to the very C-term end of CALM.

**Oncogenesis**
It is not known which of the 2 fusion proteins has the critical role.

### References


Kobayashi H, Hosoda F, Maseki N, Sakurai M, Imashuku S, Ohki M, Kaneko Y. Hematologic malignancies with the t(10;11)(p13;q21) have the same molecular event and a variety of morphologic or immunologic phenotypes. Genes Chromosomes Cancer 1997 Nov;20(3):293-9.

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

t(11;14)(q13;q32) in multiple myeloma
Jean-Loup Huret, Jean-Luc Laï

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH); INSERM Unité 524, Institut de Recherche sur le Cancer de Lille, Lille, France (JLL)

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Clinics and pathology

Disease
Multiple myeloma (MM) is a malignant plasma cell proliferation.

Phenotype / cell stem origin
Phenotype of mature differentiated B-cell, but also with CD56 expression, which is not found in normal plasma cells.

Epidemiology
Multiple myeloma's annual incidence: 30/10^6; mean age: 62 yrs; t(11;14) is found in 10-20% of cases of MM with an abnormal karyotype; t(11;14) is not found associated with particular sex or age group; found mostly in stage III MM.

Clinics
Bone pain; susceptibility to infections; renal failure; neurologic dysfunctions.

Pathology
MM staging:
- Stage I: low tumour cell mass; normal Hb; low serum calcium; no bone lesion; low monoclonal Ig rate;
- Stage II: fitting neither stage I nor stage II;
- Stage III: high tumour cell mass; low Hb and/or high serum calcium and/or advanced lytic bone lesions and/or high monoclonal Ig rate.

Prognosis
Evolution: multiple myeloma can evolve towards plasma cell leukaemia;
Prognosis (highly variable) is according to the staging and other parameters, of which are now the karyotypic findings.

Cytogenetics

Cytogenetics, morphological

- t(11;14) is balanced in most cases; some cases are: -14, +der(14)t(11;14); t(11;14) may well be a secondary event in MM, is as it has been found occurring during course of the disease.

Cytogenetics, molecular

FISH is indicated, as metaphases are arduous to obtain in such a disease implicating mature cells.

Additional anomalies

- t(11;14) is part of a complex karyotype; accompanied with -13 or del(13q) in 'only' 1/4 of cases while -13/del(13q) is found in about 40% of MM cases with an abnormal karyotype; structural (and variable) anomalies of chromosome 1 are found in 1/3 of cases with t(11;14).

Variants

Complex three way translocations t(11;Var;14) have been described.

Genes involved and Proteins

BCL1
Location: 11q13

IgH
Location: 14q32

References


This article should be referenced as such:
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- http://AtlasGeneticsOncology.org/Forms/Leukaemia_Form.html for reviews on leukaemias,
- http://AtlasGeneticsOncology.org/Forms/SolidTumour_Form.html for reviews on solid tumours,

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Case Reports in haematological malignancies are dedicated to recurrent -but rare- chromosomes abnormalities in leukaemias/lymphomas. Cases of interest shall be: 1- recurrent (i.e. the chromosome anomaly has already been described in at least 1 case), 2- rare (previously described in less than 20 cases), 3- with well documented clinics and laboratory findings, and 4- with iconography of chromosomes.

It is mandatory to use the specific "Submission form for Case reports": see http://AtlasGeneticsOncology.org/Reports/Case_Report_Submission.html.

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