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

**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

The *Atlas of Genetics and Cytogenetics in Oncology and Haematology* is published 4 times a year by ARMGHM, a non profit organisation.

Philippe Dessen is the Database Director, and Alain Bernheim the Chairman of the on-line version (Gustave Roussy Institute – Villejuif – France).

http://AtlasGeneticsOncology.org

© ATLAS - ISSN 1768-3262
## Table of contents

### Gene Section

<table>
<thead>
<tr>
<th>Gene</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR1 (fibroblast growth factor receptor 1)</td>
<td>35</td>
</tr>
<tr>
<td>LCP1 (lymphocyte cytosolic protein1)</td>
<td>36</td>
</tr>
<tr>
<td>MTCP1 (mature T cell proliferation 1)</td>
<td>37</td>
</tr>
<tr>
<td>NF2 (neurofibromin 2)</td>
<td>39</td>
</tr>
<tr>
<td>MYCN (myc myelocytomatosis viral related oncogene, neuroblastoma derived)</td>
<td>41</td>
</tr>
<tr>
<td>POU2AF1 (POU domain, class 2, associating factor 1)</td>
<td>43</td>
</tr>
<tr>
<td>ABCB1 (ATP-binding cassette, sub-family B (MDR/TAP), member 1)</td>
<td>45</td>
</tr>
<tr>
<td>TAL1 (T-cell acute leukemia 1)</td>
<td>47</td>
</tr>
<tr>
<td>TCL1 (T cell leukemia/lymphoma 1)</td>
<td>49</td>
</tr>
<tr>
<td>TCLA (T-cell leukemia translocation-associated gene)</td>
<td>51</td>
</tr>
<tr>
<td>ZNF198 (zinc finger protein 198)</td>
<td>52</td>
</tr>
</tbody>
</table>

### Leukaemia Section

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(9;12)(p24;p13)</td>
<td>54</td>
</tr>
<tr>
<td>del(9q) solely</td>
<td>55</td>
</tr>
</tbody>
</table>

Jean-Loup Huret
(Poitiers, France)
Essential thrombocythemia
Jean-Loup Huret 57

Acute basophilic leukemia; t(X;6)(p11;q23)
Nicole Dastugue 58

t(5;14)(q33;q32) PDGFRB/TRIP11
Jean-Loup Huret 59

t(11;16)(q23;p13)
Jean-Loup Huret 60

t(16;21)(p11;q22)
Christine Pérot 62

Solid Tumour Section

Nervous system: Peripheral neuroblastic tumours (Neuroblastoma,
Ganglioneuroblastoma, Ganglioneuroma)
Jérôme Couturier, Daniel Satgé 63

Cancer Prone Disease Section

Bloom syndrome
Jean-Loup Huret 65

Dubowitz syndrome
Jean-Loup Huret, Claude Léonard 67

Fanconi anaemia
Jean-Loup Huret 68
FGFR1 (fibroblast growth factor receptor 1)

Jean-Loup Huret

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

Published in Atlas Database: March 1998
Online updated version: http://AtlasGeneticsOncology.org/Genes/FGFR1113.html
DOI: 10.4267/2042/37403

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: BFGFR (basic fibroblast growth factor receptor); FLT2 (FMS-like tyrosine kinase 2); FLG (FMS-like gene); CEK; FGFRBR; N-SAM
Location: 8p11
Local order: more telomeric than MOZ.

DNA/RNA

Transcription
2.7 mRNA.

Protein

Description
822 amino acids; 100-135 kDa glycoprotein from a 90-115 kDa protein core; tyrosine kinase receptor; contains three major domains: an extracellular domain with 3 Ig-like loops, a transmembrane domain and an intracellular domain with tyrosine kinase activity.

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 (FGFR2, FGFR3, and FGFR4).

Implicated in

t(8;13)(p12;q12)/ANLL-NHL → ZNF198/FGFR1

Disease
Combined myeloid malignancy and T-cell NHL.

Prognosis
Very poor (median survival: 12 mths).

Cytogenetics
Additional anomalies: +8, +der(13), +21.

Hybrid/Mutated Gene
5’ ZNF198 - 3’ FGFR1.

Abnormal Protein
N-term zinc fingers from ZNF198 fused to the Tyrosine kinase domain of FGFR1 in C-term.

Oncogenesis
Constitutive activation of FGFR1.

Pfeiffer syndrome (inborn disease)

Disease
One form of Pfeiffer syndrome, an autosomal dominant craniosynostosis syndrome with broad thumbs and usually no mental deficiency, is due to a mutation in amino acid 252 of FGFR1.

References


Itoh N, Terachi T, Ohta M, Seo MK. The complete amino acid sequence of the shorter form of human basic fibroblast growth factor receptor deduced from its cDNA. Biochem Biophys Res Commun 1990;169:680-685.


This article should be referenced as such:
LCP1 (lymphocyte cytosolic protein1)
Sylvie Galiègue-Zouitina

Published in Atlas Database: March 1998
Online updated version: http://AtlasGeneticsOncology.org/Genes/LCP1ID95.html
DOI: 10.4267/2042/37404

Identity
Other names: L-Plastine
Location: 13q14

DNA/RNA
Description
Spans on a 90 kb genomic fragment; 16 exons, large first intron (20 kb).

Transcription
3.7 kb mRNA; coding sequence from exon 2 to exon 16: 3500 bp.

Protein
Description
570 amino acids.

Expression
Restricted to the hematopoietic cells (leukocytes); expression induced in all tumor cells of all tissues.

Localisation
Membrane.

Homology
Belongs to an actin-binding protein family (T-Plastin, Fimbrin, I-Plastin).

Implicated in
\[ t(3;13)(q27;q14)/NHL \rightarrow LCP1/ BCL6 \]

Disease
Non Hodgkin follicular as well as Burkitt lymphomas.

Cytogenetics
t(3;13) is observed as a secondary anomaly.

Hybrid/Mutated Gene
Both 5' L-Plastin- 3' BCL6 and 5' BCL6 - 3' L-Plastin, leading to two fusion transcripts.

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

References


This article should be referenced as such:
MTCP1 (mature T cell proliferation 1)
Marc-Henri Stern

Unité INSERM U462, Centre Hayem, Hopital Saint Louis, 75475 Paris Cedex 10, France

Published in Atlas Database: March 1998
Online updated version: http://AtlasGeneticsOncology.org/Genes/MTCP1ID89.html
DOI: 10.4267/2042/37405

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: C6.1B
Location: Xq28
Local order: Centromere- Factor VIII - c6.1A - MTCP1 - telomere.

DNA/RNA

MTCP1 (Xq28) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact rocchi@biologia.uniba.it.

Protein

Description
p8 MTCP1: coded by transcripts A, 68 amino acids; one domain formed by 3 alpha helices held together by two disulphide bridges in an antiparallel coiled-coil motif.

Expression
Ubiquitously expressed.

Localisation
Mitochondrial.

Function
Unknown.

Homology
None.

Description
p13 MTCP1: coded by transcripts B, 107 amino acids; one domain with a b-barrel topology.

Expression
Protein expression undetectable in physiological conditions.

Localisation
Cytosol.

Function
Unknown.

Homology
TCL1 (39% identity, similar tridimensional structure).
Implicated in

\[ t(X;14)(q28;q12)/\text{prolymphocytic leukaemia} \rightarrow \text{TCRA-D/MTCP1} \]

**Disease**
T-cell prolymphocytic leukaemia.

**Cytogenetics**
Associated with i(8q).

**Hybrid/Mutated Gene**
Unconstant TCRA-c6.1A transcripts have been described.

**Abnormal Protein**
None.

**Oncogenesis**
Overexpression of p13 MTCP1 is considered as critical in the oncogenetic mechanism.

\[ t(X;7)(q28;q35)/\text{prolymphocytic leukaemia} \rightarrow \text{TCRB/MTCP1} \]

**Disease**
T-cell prolymphocytic leukaemia.

**Oncogenesis**
Overexpression of p13 MTCP1.

**References**


This article should be referenced as such:
**NF2 (neurofibromin 2)**

Jean-Loup Huret

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

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/NF2117.html

DOI: 10.4267/2042/37406

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

**Identity**

Other names: SCH (schwannoma)

Location: 22q12.1-12.2 junction, incidentally not far from EWS.

**DNA/RNA**

Description

16 exons; spans 120 kb; open reading frame: 1.8 kb.

Transcription

Alternate splicings, in particular after exon 15.

**Protein**

Description

Called merlin, schwannomin, or SCH; 590 or 595 amino acids; 66 kDa; NH2 -- membrane binding -- large a helix domain binding to actin of the cytoskeleton -- COOH

Expression

Wide: in lung, kidney, ovary, breast, placenta, neuroblasts; high in fetal brain.

Localisation

Membrane associated.

Function

Membrane-cytoskeleton anchor (as APC also appears to be); role in the development of extraembryonic structures before gastrulation; has characteristics of a tumour suppressor, as has been found in sporadic as well as neurofibromatosis type 2 induced schwannomas and meningiomas.

Homology

Ezrin, talin, radixin, moesin, members of the erythrocytes band 4.1 family, especially in the N-term.

**Mutations**

Germinal

Inborn condition of neurofibromatosis type 2 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. those severe phenotypes are found in cases with protein truncations rather than those with amino acid substitution).

Somatic

Mutation and allele loss events in tumours in neurofibromatosis type 2 and in sporadic schwannomas and meningiomas are in accordance with the two-hit model for neoplasia, as is found in retinoblastoma.

**Implicated in**

Neurofibromatosis type 2

Disease

Autosomal dominant cancer prone disease; neurofibromatosis type 2 (NF2: the same symbol is used for the disease neurofibromatosis type 2 and the gene neurofibromin 2) is a hamartoneoplastic syndrome.

Prognosis

Hamartomas have a potential towards neoplasia; those, in NF2, are schwannomas and meningiomas.

Sporadic meningioma

Sporadic schwannoma

Other tumours

Ependymoma; mesothelioma.

**References**

Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C,
NF2 (neurofibromatosis type 2) Huret JL


This article should be referenced as such:
Gene Section
Mini Review

MYCN (myc myelocytomatosis viral related oncogene, neuroblastoma derived)

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

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/NMYC112.html
DOI: 10.4267/2042/37407

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

MYCN (2p24) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact rocchi@biologia.uniba.it.

Location: 2p24.1
Local order: centromeric to DDX1

DNA/RNA

Description
3 exons.

Protein

Description
464 amino acids; contains a phosphorylation site, an acidic domain, an HLH motif, and a leucine zipper in C-term; forms heterodimers with MAX and recognize the core consensus sequence CACCTG.

Expression
During fetal development.

Localisation
Nuclear.

Function
Probable transcription factor; possible role during tissue differentiation.

Homology
With members of the myc family of helix-loop-helix transcription factors.
Mutations

Somatic
Amplification, either in extrachromosomal double minutes or in homogeneously staining regions within chromosomes (there is amplification when, for example, 10 to 1000 copies of a gene are present in a cell); found amplified in a variety of human tumours, in particular in and also in retinoblastoma, small cell lung carcinoma, astrocytoma; level of amplification related to the tumour progression; transgenic mice that overexpress MYCN in neuroectodermal cells develop neuroblastoma.

Implicated in

Neuroblastoma
Oncogenesis
MYCN amplification is found in 15% of neuroblastoma, is an adverse prognostic feature per se, and is often associated with other adverse features (older age, abdominal tumour, advanced disease, and high lactate dehydrogenase, ferritin, and neuron-specific enolase serum levels).

References


This article should be referenced as such:

POU2AF1 (POU domain, class 2, associating factor 1)

Sylvie Galiègue-Zouitina

U.124 INSERM, I.R.C.L., Place de Verdun, 59045 Lille Cedex, France

Published in Atlas Database: March 1998
Online updated version: http://AtlasGeneticsOncology.org/Genes/OBF94.html
DOI: 10.4267/2042/37408

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: BOB1; OCA-B; POU2AF1 (POU domain, class 2, associating factor 1)
Location: 11q23.1
Local order: telomeric to ATM.

DNA/RNA

POU2AF1 (11q23) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome.

Description
Spans on a 30 kb genomic fragment; five exons; large fifth exon, with many 3'-UTR repetitive elements, two pyrimidine rich regions (a duplicated CT-rich region and a [CCTT]n tetranucleotide tandem repeat) and a 282 nucleotides long Alu element.

Transcription
3.4 kb mRNA; coding sequence: 770 bp, spanning from the end of exon 1 to the beginning of exon 5.

Protein

Description
256 amino acids; 27.4 kDa; proline rich protein with no recognizable domain or motifs.

Expression
Constitutively expressed in B-cells and inducible in T-cells.

Localisation
Nuclear.

Function
B-cell specific transcriptional coactivator: involved in the transcription of immunoglobulin genes through recruitment to the highly conserved octamer site of immunoglobulin promoters, mediated by either Oct-1 or Oct-2 transcription factor; forms a ternary complex on DNA together with either Oct-1 or Oct-2 transcription factor; is essential for the response of B-cells to antigens and is required for the formation of germinal centres.

Homology
No homology to known proteins.

Implicated in

\( t(3;11)(q27;q23.1)/NHL \rightarrow BCL6/OBF1 \)

Disease
NHL.
Cytogenetics
Found in complex karyotypes.

Hybrid/Mutated Gene
5’ BOB1 - 3’ BCL6 and 5’ BCL6 - 3’ BOB1, leading to two fusion transcripts.

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

References

This article should be referenced as such:
Gene Section

Mini Review

ABCB1 (ATP-binding cassette, sub-family B (MDR/TAP), member 1)

Franck Viguié

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

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/PGY1ID105.html

DOI: 10.4267/2042/37409

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: MDR1 (multidrug resistance 1)
Location: 7q21.2

DNA/RNA

Description
Spans on a 120 kb genomic fragment; separated from MDR3 gene (which is transcribed in the same direction) by only 34 kb of intergenic DNA.

Transcription
5 kb mRNA.

Protein

Description
The protein is called P-glycoprotein; 170 kDa transmembrane glycoprotein which includes 10-15 kDa of N-term glycosylation; the N-term half of the molecule contains 6 transmembrane domains, followed by a large cytoplasmic domain with an ATP binding site, and then a second section with 6 transmembrane domains and an ATP binding site which shows over 65% of amino acid similarity with the first half of the polypeptide.

Expression
Normally expressed at secretory surface of a number of tissues, including biliary canaliculi, proximal tubules of the kidney, intestinal and colonic epithelium; hematopoietic stem cells express high levels of P-glycoprotein; overexpressed in many multidrug resistant cell lines and in tumour cells resistant to chemotherapy.

Localisation
Mainly at the cell membrane, with a secondary localisation at the Golgi apparatus.

Function
The P-glycoprotein is an energy-dependent efflux pump involved in extrusion of many types of lipophilic compounds; it may acts in normal tissues as a protective mechanism against noxious xenobiotics and as a transporter of endogenous substrates; in tumour cells, the drug efflux pump results in a decrease in intracellular drug concentration.

Homology
Closely related gene to MDR3 (also called PGY3), located at the same chromosomal site but not implicated in multidrug resistance; there are 3 murine homolog genes (mdr1, mdr2, mdr3) out of which only 2 (mdr1 and mdr3) are involved in multidrug resistance; member of a large superfamily of transmembrane transporter proteins named ATP Binding Cassette (ABC) transporters or Traffic ATPases; structural homology with other ABC transporter proteins (CFTR, MRP).

Implicated in

Tumour cells resistance

Disease
Tumour cells resistance to a wide variety of antineoplastic agents: doxorubicin, daunorubicin, vinblastine, vincristine, colchicine, actinomycine D, etoposide, teniposide, mitoxantrone, homoharringtonine; this phenomenon is named 'multidrug resistance' (MDR); P-glycoprotein is the main protein responsible for the MDR phenotype;
however, other agents may be involved in MDR, independently or in association with P-glycoprotein: "multidrug resistant associated protein" (MRP), "lung resistance protein" (LRP), "anthracycline associated resistance protein" (ARX).

**Leukemias**

**Disease**

In leukemia, MDR1 overexpression is observed in patients with a lower complete remission rate and with a shortening of overall survival; frequently associated with intermediate and poor prognosis karyotype; in ANLL, approximately 50% of patients are MDR positive at diagnosis (range 22-70%) and the MDR phenotype is more frequently observed in CD34+ leukemias; in ALL, the average number of MDR-positive cases is 22% at diagnosis.

**Tumour cell lines**

**Note**

In numerous continuous tumour cell lines which acquired experimentally a MDR phenotype when cultured with progressively increasing drug concentration, the acquisition of MDR was associated with hyperexpression of P-glycoprotein; for the higher levels of expression, southern blots revealed an increase in the number of copies of the MDR1 gene per cell.

**Cytogenetics**

The genomic amplification of MDR1 appears as extrachromosomal ‘double-minute chromosomes’ (DM) or intrachromosomal ‘homogeneous staining regions’ (HSR).

**Oncogenesis**

Amplification.

**References**


Schoenlein PV, Shen DW, Barrett JT, Pastan I, Gottesman MM. Double minute chromosomes carrying the human multidrug resistance 1 and 2 genes are generated from the dimerization of submicroscopic circular DNAs in colchicine-selected KB carcinoma cells. Mol Biol Cell 1992 May;3(5):507-20.


This article should be referenced as such:

**Gene Section**

**Mini Review**

**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)

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/TAL1.html

DOI: 10.4267/2042/37410


This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

**Identity**

**Other names:** SCL (stem cell leukaemia), TCL5 (T cell leukaemia 5)

**Location:** 1p32

**DNA/RNA**

![DNA diagram]

**Description**

8 exons; 16 kb; SIL (a different gene) sits 90 kb further in 5'.

**Transcription**

(Complex) alternate splicing of: 1A with 2A, or 3 vs 1B, 2B, 3... or directly 4, 5, 6.

**Protein**

**Description**

331 amino acids for the major form of 48 kDa; a truncated form of 26 kDa only in some T-ALL; domains: prolin rich in N-term; poly Gly; basic Helix-Loop-Helix from the exon 6.

**Expression**

In hematopoietic stem cells, erythroid and megakaryocytic lineages of the adult and in the embryonic brain; indispensable for the genesis of the hematopoietic system.

**Function**

Transcription factor; exhibits sequence-specific DNA binding activity when in dimers with another bHLH protein such as E2A (DNA specific sequences are: CANNTG, especially: CAGATG); direct interactions of the bHLH with the LIM domain of RBTN2 or RBTN1.

**Homology**

TAL2 in 9q32; LYL1 in 19p13; more distantly: MYC and other members of the MYC family of Helix-Loop-Helix transcription factors.

**Implicated in**

\[
\begin{align*}
t(1;7)(p32;q34) & \text{ or } t(1;14)(p32;q11)/T-ALL \\
& \rightarrow TAL1/TCRB \text{ or } TAL1/TCRD
\end{align*}
\]

**Disease**

T-cell ALL.

**Prognosis**

Is not too poor, compared to other T-ALL.

**T-ALL with normal karyotype, but with submicroscopic deletions of part of TAL1 in the 5' region → SIL/TAL1**

**Disease**

Found in 10 to 30% of T-ALL with a normal karyotype.

**Hybrid/Mutated Gene**

Deletions which place SIL (SCL interrupting sequence) in close 5' of TAL1; hybrid gene with exon 1 from SIL.

**Abnormal Protein**

TAL1 is under the promoter sequences controle of SIL, a gene active during T cell development.

\[
\begin{align*}
t(1;3)(p32;p21)/T-ALL & \rightarrow TAL1/TCTA
\end{align*}
\]

**Disease**

T-cell ALL.
Breakpoints

Note: mainly in 5' in a 1 kb region; but also dispersed in rare cases.

References


Ono Y, Fukuhara N, Yoshie 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:

TCL1 (T cell leukemia/lymphoma 1)
Marc-Henri Stern
Unité INSERM U462, Centre Hayem, Hopital Saint Louis, 75475 Paris Cedex 10, France

Published in Atlas Database: March 1998
Online updated version: http://AtlasGeneticsOncology.org/Genes/TCL1ID66.html
DOI: 10.4267/2042/37411

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity
Location: 14q32.1

DNA/RNA
Description
4 exons; telomere - exon 1 to 4 - centromere orientation.

Transcription
1.3 kb transcripts.

Protein
Description
114 amino acids; one domain with a b-barrel topology.

Expression
Immature T and B lymphoid cells.

Localisation
Cytoplasm.

Function
Unknown.

Homology
MTCP1 (38 % identity, similar tridimensional structure).

Implicated in

\[ t(14;14)(q12;q32.1) \] or \[ \text{inv}(14)(q12q32.1) / \text{T-cell malignancies} \]
\[ \rightarrow \text{TCRA/D/TCL1} \]

Disease
Mainly T-cell prolymphocytic leukemia (T-PLL); T-cell NHL; T-cell ALL.

Cytogenetics
Associated with i(8q) in T-PLL.

Hybrid/Mutated Gene
None.

Abnormal Protein
None.

Oncogenesis
Over expression of TCL1 is considered as critical in the oncogenetic mechanism.

\[ t(7;14)(q35;q32.1) / \text{T-cell malignancies} \]
\[ \rightarrow \text{TCRB/TCL1} \]

Disease
Mainly T-cell prolymphocytic leukemia.

Cytogenetics
Associated with i(8q).

Hybrid/Mutated Gene
None.

Abnormal Protein
None.

Oncogenesis
Over expression of TCL1.

References


This article should be referenced as such:
TCTA (T-cell leukemia translocation-associated gene)

Jean-Loup Huret

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

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/TCTA.html

DOI: 10.4267/2042/37412

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

### Identity

**Location:** 3p21

### DNA/RNA

- **Transcription:** 2.1 kb mRNA.

### Protein

**Description:** 103 amino acids; 11 kDa; rich in hydrophobic amino acids (residues 41-61).

**Expression:** Wide, especially in kidneys.

**Localisation:** May be a membrane associated protein, as there is a hydrophobic domain.

**Function:** Unknown.

### Homology

None is known.

### Implicated in

\[ t(1;3)(p32;p21)/T-cell ALL \rightarrow TAL1/TCTA \]

### Disease

T-cell ALL.

### Hybrid/Mutated Gene

Head to head orientation of TAL1 and TCTA.

### Abnormal Protein

No fusion protein, but possibly promoter exchange and gene disregulation.

### To be noted

**Note:** on day 04 Feb 1998, nothing new has appeared since the above coted paper.

### References


This article should be referenced as such:

# ZNF198 (zinc finger protein 198)

## Jean-Loup Huret, Dominique Leroux

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH); Lymphoma Research Group - Groupe de Recherche sur les Lymphomes, Institut Albert Bonniot, La Tronche 38706, France (DL)

Published in Atlas Database: March 1998

Online updated version: http://AtlasGeneticsOncology.org/Genes/ZNF198ID114.html

DOI: 10.4267/2042/37413

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence. © 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

<table>
<thead>
<tr>
<th>Identity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other names:</strong> FIM (fused in myeloproliferative disorders)</td>
</tr>
<tr>
<td><strong>Location:</strong> 13q12</td>
</tr>
<tr>
<td><strong>Local order:</strong> proximal from FLT1 and FLT3.</td>
</tr>
</tbody>
</table>

FIM (13q12) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics. Laboratories willing to validate the probes are welcome: contact rocchi@biologia.uniba.it.

<table>
<thead>
<tr>
<th>DNA/RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>5.0 kb cDNA; coding sequence: 4.1 (formerly 2.7 kb).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transcription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main transcripts: 5.0 and 7.5 kb.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>1379 amino acids; 4 zinc fingers in N-term, a highly hydrophobic proline repeat, and a C-term acidic domain.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wide.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Homology</th>
</tr>
</thead>
<tbody>
<tr>
<td>With DXS6673E, a gene which may be related with mental retardation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Implicated in</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;13)(p12;q12)/ANLL-NHL → 5'</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ZNF198 - 3' FGFR1</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Hybrid/Mutated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>5' ZNF198 - 3' FGFR1</td>
</tr>
</tbody>
</table>

### Disease
Combined myeloid malignancy and T-cell NHL.

### Prognosis
Very poor (median survival: 12 mths).

### Cytogenetics
Additional anomalies: +8, +der(13), +21.
Abnormal Protein
N-term zinc fingers from ZNF198 fused to the Tyrosine kinase domain of FGFR1 in C-term.

Oncogenesis
Constitutive activation of FGFR1.

References

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

$t(9;12)(p24;p13)$
Jean-Loup Huret

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

Published in Atlas Database: February 1998
Online updated version: http://AtlasGeneticsOncology.org/Anomalies/1122t0912.html
DOI: 10.4267/2042/37414

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Clinics and pathology

Disease
Acute leukaemias; poorly known: only 3 available cases, and with different phenotypes: a T-cell ALL, a CD10+-ALL, and a 'CML-like' disease in transformation; all 3 were male patients.

Genes involved and Proteins

$JAK2$
Location: 9p24
DNA / RNA
24 exons.
Protein
Tyrosine kinase; possibly membrane associated; signal transduction.

$ETV6$
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’ JAK2.

Fusion protein
Description
N-term- HLH oligomerization domain from ETV6 fused to the tyrosine kinase C-term domains of JAK2 (or even starting with the JH2); the reciprocal JAK2-ETV6 may not be expressed.

Oncogenesis
It may be speculated that the HLH domain of ETV6 induces oligomerization, resulting in constitutive activation of the kinase domain of JAK2.

References

This article should be referenced as such:
Leukaemia Section

Mini Review

del(9q) solely
Franck Viguié

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

Published in Atlas Database: February 1998

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/del9q.html
DOI: 10.4267/2042/37415

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

del(9q) G-banding - Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap Cytogenetics at the Waisman Center (left and middle) and Jean-Luc Lai (right).

Note: del(9q) as the sole abnormality must be distinguished from syndromes where it is associated with other chromosome rearrangements; in particular, there is frequent association with LAM2 expressing t(8;21)(q22;q22), and, also, with t(15;17)(q24;q21); we herein describe del(9q) as the sole anomaly, when not otherwise specified.

Clinics and pathology

Disease
ANLL mainly; rarely observed in myelodysplastic syndroms (MDS) or myeloproliferative disorders; biphenotypic T-lymphoid / myeloid leukemias cases have also been described.

Phenotype / cell stem origin
ANLL: M1, M2, M4, M6 FAB subtypes; pluripotent stem cell probably involved; there is a trilineage myelodysplasia; six patients (4 M1, 1 M2 and 1 T-ALL) from two reports have been described with del(9q) and CD34+, CD7+, T lymphoid / myeloid biphenotypic leukemia.

Epidemiology
0 to 3% of ANLL cases, depending on series; both sexes equally represented; adults and children may be affected.

Cytology
Frequent sideroblasts; leukemic blasts are agranular, with large vacuoles on Giemsa staining and localized positivity for myeloperoxidase (MPO); giant MPO positive granules are described, corresponding to = AB pseudo-Chediak-Higashi ==BB granules; most blast cells are CD34 positive.

Prognosis
When del(9q) is the unique chromosome abnormality the prognosis, depending on AML subtype, is variable; (del(9q) as a secondary anomaly in t(8;21) has no prognostic consequence for some workers and is a factor of worse prognosis for others).
**Cytogenetics**

**Cytogenetics, morphological**
Interstitial deletion of chromosome 9 long arm, called del(9q) or 9q-, involving a variable chromosome segment; the region 9q21-22 seems constantly involved.

**Cytogenetics, molecular**
This constantly deleted region has not yet been more precisely defined and it is not known whether deletion of one or more critical gene(s) are involved. Thus there are presently no 9q molecular probes available to assess 9q deletion.

**Probes**
Whole chromosome 9 painting, to exclude 9q translocations.

**Additional anomalies**
On 31 reviewed cases of ANLL with del(9q) as a primary change, none had additional anomalies del(9q) as a secondary anomaly:
- Association with t(8;21) represents the majority of cases; t(8;21) occurs in 5 to 10 % of patients with ANLL, and its association with del(9q) is the second more frequent, after the association with loss of one sex chromosome; it represents approximately 10-15 % of cases.
- Association with t(15;17), in promyelocytic leukemia, has also seldom (1%) been observed.
- In these two syndromes, del(9q) is usually not present at diagnosis but appears as an additional change at relapse.
- del(9q) has never been described in association with other recurrent primary changes.

**Variants**
Unbalanced translocations involving 9q may, in a way, be considered as del(9q) variants.

**Genes involved and Proteins**

**Note:** genes involved are unknown; there is probable deletion of one or several tumor suppressor gene(s) involved in the progression of the disease.

**References**


Kwong YL, Chan TK, Chan LC. Interstitial deletion of the long arm of chromosome 9 as the sole anomaly in acute myeloid leukaemia is associated with dyserythropoiesis. Leukemia 1992 Jun;6(1):64-5.


This article should be referenced as such:
Essential thrombocythemia

Jean-Loup Huret

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

Published in Atlas Database: February 1998

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/ET.html

DOI: 10.4267/2042/37416

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Clinics and pathology

Disease
Chronic myeloproliferative syndrome.

Phenotype / cell stem origin
Pluripotent stem cell is involved.

Epidemiology
Annual incidence is less than 1/10^6; sex ratio 1M/; median age 50-60 years.

Clinics
Often revealed by haemorrhages or thrombosis; splenomegaly is found in 50% of cases; blood data: the disease is defined by a thrombocytosis > 600 X 10^9 L; the platelet count is actually often > 1000 X 10^9 L.

Prognosis
Evolution: chronic disease; can evolve towards polycytemia vera or myelofibrosis, seldom towards ANLL; prognosis: often fair, is variable according to age and depends on haemorrhages, thromboses, and embolisms, which are the major causes of death in this disease.

Cytogenetics

Cytogenetics, morphological
A normal karyotype is found in 95% of cases; +9 is the only anomaly having been described in as far as 4 cases!

Genes involved and Proteins

Note: genes involved are unknown.

References


This article should be referenced as such:
Acute basophilic leukemia
t(X;6)(p11;q23)
Nicole Dastugue
Génétique des Hémopathies, Laboratoire d'Hématologie, Hôpital Purpan, 31000, Toulouse Cedex, France

Disease
Rare type of acute myeloid leukemia.

Phenotype / cell stem origin
Basophilic precursor.

Epidemiology
Very rare but might be prominent in infants.

Clinics
Hyperhistaminemia syndrome has been reported in some of the cases.

Cytology
Major component of undifferentiated blasts + minor component of basophilic blasts (blasts containing large granules reacting positively to toluidine blue staining).

Treatment
ANLL protocols.

Prognosis
Good response to standard therapy for childhood ANLL.

Cytogenetics

Cytogenetics, morphological
t(X;6)(p11;q23)

Cytogenetics, molecular
Not done.

Genes involved and Proteins
Note: are unknown.

References

This article should be referenced as such:
t(5;14)(q33;q32) PDGFRB/TRIP11

Jean-Loup Huret

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

Published in Atlas Database: February 1998
Online updated version: http://AtlasGeneticsOncology.org/Anomalies/t0514ANL.html
DOI: 10.4267/2042/37418

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Leukaemia Section
Short Communication

Clinics and pathology

Disease
Yet poorly known: 1 case of ANLL.

Clinics
Found at relapse with eosinophilia of a M2 ANLL with t(7;11).

Cytogenetics

Cytogenetics, morphological
So far found as an additional anomaly in a clone bearing a t(7;11)(p15;p15).

Genes involved and Proteins

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

CEV14
Location: 14q32
Protein
Contains a N-term leucine zipper and a C-term putative thyroid hormone receptor interacting domain.

Results of the chromosomal anomaly

Hybrid gene
Description
5' CEV14 - 3' PDGFRb

Transcript
10 kb fusion transcript (major) and other (minor) transcripts.

Fusion protein
Description
N-term leucine zipper from CEV14 fused to the transmembrane domain and the Tyr kinase domain of PDGFRb in C-term; the reciprocal transcript is not expressed; breakpoints at amino acids 1936 of PDGFRb and 567 of CEV14.

Oncogenesis
Ectopic constitutive tyrosine kinase activation of PDGFRb may occur.

To be noted
The above t(5;14)(q33;q32) with PDGFRb and CEV14 rearrangements must not be confused with the t(5;14)(q31;q32) with IL3 and IgH involvements found in ALL.

References

This article should be referenced as such:
t(11;16)(q23;p13)

Jean-Loup Huret

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

Clinics and pathology

Disease
ANLL/MDS: only treatment related leukaemias cases so far (in other 11q23 translocations, most cases occur in de novo acute leukaemia).

Phenotype / cell stem origin
M4, M2 ANLL; CMML and RAEBT, although MDS is otherwise rarely seen in 11q23 translocations; the fusion gene is found in all the mature monocytes, in some of the granulocytes and erythroblasts, not in the lymphocytes.

Epidemiology
13 available cases; most cases are children cases: median age is 10-14 yrs, range is 2-74 yrs; sex ratio is balanced.

Clinics
Secondary to antitopoisoemerase II drugs (etoposide or teniposide, but also doxorubicin); this secondary malignancy occurs within 6-60 mths (median 20 mths); the primary malignancy was a t(8;21)(q22;q22)/M2-ANLL in 2 cases.

Prognosis
Yet unknown.

Cytogenetics

Additional anomalies
Are found in 8 of 11 cases; variable, except the unexpecteted recurrence of 1p36.1 involvement.

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; transcriptional regulatory factor; nuclear localisation.

CBP
Location: 16p13

Protein
Nuclear localisation; transcriptional adaptor/coactivator: binds CREB; has histone acetyltransferase activity.

Results of the chromosomal anomaly

Hybrid gene
Description
5’ MLL - 3’ CBP

Fusion protein
Description
N-term AT hook and DNA methyltransferase from MLL fused to most of CBP starting with the bromodomain of CBP -or even more in N-term with the CREB binding domain- and also comprising the cystein/histidine rich and the glutamine rich domains of CBP in C-term around 1400 amino acids from MLL; the reciprocal CBP-MLL may or may not be expressed.

Oncogenesis
May promote histone acetylation of genomic regions targeted by the MLL AT-hooks; may loose CBP cell cycle inhibition capability.
References


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

\( t(16;21)(p11;q22) \)
Christine Pérot
Laboratoire de Cytogenetique, Hopital Saint-Antoine, Paris, France

Published in Atlas Database: February 1998
Online updated version: http://AtlasGeneticsOncology.org/Anomalies/t1621.html
DOI: 10.4267/2042/37420

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.
© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Clinics and pathology

Disease
De novo ANLL; (one case of blast crisis CML).

Phenotype / cell stem origin
Mainly M2 or M4, but also M1, M5a, M5b, or M7 ANLL; may be preceded by MDS.

Epidemiology
About 30 reported cases, mainly found in young adults; children cases are described; median age is about 30 yrs; balanced sex ratio.

Clinics
Blood data: anemia, thrombocytopenia, mild hyperleucocytosis; with high monocyctic cell count at times.

Cytology
Myelocytic and monocytoid features are often present; eosinophils in the bone marrow are sometimes abnormal and/or elevated; erythrophagocytosis may be found.

Prognosis
Seems poor: complete remission may not be achieved; there is high incidence of relapse within a year and a median of survival is about 22 months (cases herein reviewed).

Cytogenetics

Additional anomalies
Rarely found solely; most often associated with various numerical or structural abnormalities; trisomy 10 was found in 4 of 17 cases.

Genes involved and Proteins

FUS
Location: 16p11

ERG
Location: 21q22

Results of the chromosomal anomaly

Hybrid gene
Description
5’ FUS - 3’ ERG

Fusion protein
Description
N-term FUS RNA binding domain fused to the C-term DNA binding ETS domain of ERG.

Oncogenesis
Seems to act as a transcriptional activator.

References


This article should be referenced as such:
Nervous system: Peripheral neuroblastic tumours (Neuroblastoma, Ganglioneuroblastoma, Ganglioneuroma)

Jérôme Couturier, Daniel Satgé

Department of Pathology, Institut Curie, Paris, France

Published in Atlas Database: February 1998

Online updated version is available from: http://AtlasGeneticsOncology.org/Tumors/neurob5002.html

DOI: 10.4267/2042/37421

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

**Identity**

**Note:** belongs to the group of 'small blue round cell' tumours of the children, and differential diagnosis with primitive neuroectodermal tumours (PNET), lymphoma, Ewing's tumour, and rhabdomyosarcoma may be difficult.

**Clinics and pathology**

**Disease**

Tumour of the sympathetic nervous system: medulloadrenal gland (50%), abdominal (25%), thoracic (15%), cervical or pelvic paraspinal ganglia; metastatic at diagnosis in 60% of cases (lymph nodes, bones and bone marrow, liver, skin).

**Embryonic origin**

Neural crest cells.

**Etiology**

Unknown; possible excess in neurofibromatosis type I, Wiedemann-Beckwith syndrome, and maternal exposure to phenyl hydantoin; exceptional familial cases.

**Epidemiology**

Incidence is 5-10 per million children per yr; 10% of cancers in childhood; half cases by the age of 2 yrs, 90% before 6 yrs.

**Clinics**

Presenting signs are according to the localization of the tumoural mass; high catecholamin excretion.

**Pathology**

Tumours may exhibit various degrees of differentiation:

1- Neuroblastoma: undifferentiated cells that may be arranged in rosettes surrounding a fibrillar centre;  
2- Ganglioneuroblastoma: presenting with more fibrillar material and a mixture of the above described with >50% of more mature cells;  
3- Ganglioneuroma composed of well differentiated ganglion cells and Schwann cells; a given tumour may contain more and less mature cell areas.

**Staging (Evans):**

Stage I: confined to the organ or structure of origin,  
Stage II: extending beyond the organ, but not crossing the midline (e.g. homolateral lymph nodes may be involved),  
Stage III: extending and crossing the midline,  
Stage IV: distant metastases,  
Stage IVs: stage I or II otherwise in children aged < 1 yr, with metastases in: liver, skin, bone marrow, but not in the bones.

**Treatment**

Surgery and/or radiation therapy, and/or chemotherapy.

**Evolution**

Spontaneous (and treatment induced) regression or differentiation into benign cells (ganglioneuroma) occurs rarely in tumours (mainly in infant cases).

**Prognosis**

Prognosis is very poor in most cases (median survival 1 yr); good outcome (90%) only for patients with lymph nodes negative for tumour (POG stage A); younger patients have better outcome than older patients; cytogenetic and genetic anomalies are of important prognostic value (see below).
Nervous system: Peripheral neuroblastic tumours (Neuroblastoma, Ganglioneuroblastoma, Ganglioneuroma) Couturier J, Satgé D


Genetics

Note: heterogenous disease from the genetic viewpoint; 90% cases exhibit genetic abnormalities.

Cytogenetics

**Morphological cytogenetics**

Two types can be delineated according to ploidy:
- Aneuploid tumours (near triploid, pentaploid or hexaploid), with whole chromosome anomalies, often with relative gains of chromosomes 17, 7, 6, relative losses of chromosomes 11, 14, X (molecular cytogenetics: detection with comparative genomic hybridization (CGH)); these are low grade tumours, with good prognosis.
- Diploid and/or tetraploid tumours, with del(1p) - minimal critical region being 1p36- in 40% cases, del(11q), partial trisomy for 17q21-qter (in 90% of high grade tumours), DM or HSR (N-myc amplification); these anomalies are often associated, found in high grade tumours, and bear a grave prognosis.

**Genes involved and Proteins**

**MYCN**

Location: 2p24

Protein

Nuclear protein; contains a helix-loop-helix and a leucine zipper; transcription factor.

Result of the chromosomal anomaly

**Fusion protein**

Oncogenesis

Amplification of NMYC is found in various tumours, in particular neuroblastoma; the level of amplification increases with tumour progression.

To be noted

Screening programs in several countries could not induce a fall in mortality

References


This article should be referenced as such:

Bloom syndrome

Jean-Loup Huret

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

Published in Atlas Database: February 1998

Online updated version is available from: http://AtlasGeneticsOncology.org/Kprones/BLO10002.html

DOI: 10.4267/2042/37422

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Inheritance: autosomal recessive; frequency is about 2/10^5 newborns in Ashkenazi Jews and in the Japanese (founder effect: affected persons descent from a common ancestor); much rarer otherwise.

Clinics

Note: 168 cases have been registered in the Bloom's syndrome Registry by James German; BS patients are predisposed to all types of cancer observed in the general population; thus, BS is a model of initiation and promotion of cancer, and highlights internal causes/processes of cancers.

Phenotype and clinics

- Phenotypic spectrum variable.
- Growth: dwarfism; intrauterine growth retardation; birth weight: below 2.3 kg; mean length: 44 cm; adult length < 145 cm;
- Skin: hyperpigmented (café au lait) spots; hypopigmented areas; sun sensitive telangiectatic erythema; in butterfly configuration across the face: resembles lupus erythematosus;
- Head: microcephaly; dolichocephaly; narrow face; prominent nose and/or ears; characteristic high-pitched voice;
- Normal intelligence;
- Immune deficiency → frequent infections (may be life-threatening);
- Other: myocardopathy; hypogonadism in male patients; hypertriglyceridemia.

Neoplastic risk

Nearly half of patients have had at least one cancer (10% of whom having had more than one primary cancer, which is quite characteristic of Bloom's); mean age at first cancer onset: 25 yrs (range: 2-49 yrs).
- Acute leukaemias (ALL and ANLL) in 15 % of cases; lymphomas in 15 % as well; these occur mainly before the thirties.
- Carcinomas (of a wide variety) occur in 30 % of cases, mainly after the age of 20 yrs.
- Benign tumours (10%).

Evolution

Major medical complications apart from cancers are: chronic lung disease, and diabetes mellitus (in 10 %).

Prognosis

1/3 of patients are dead at mean age 24 yrs (oldest died at 49 yrs, youngest died before 1 yr) and the mean age of the 2/3 remaining alive patients is 22 yrs (range: 4-46 yrs).

Cytogenetics

Inborn condition

- Chromatid/chromosome breaks; triradial and quadriradial figures, in particular symmetrical quadriradial configuration involving homologous chromosomes (Class I q), which are pathognomonic and which may be due to a mitotic crossing-over; found in 3-4% of metaphases (normal: 1/10^5).
- Diagnosis is on the (pathognomonic) highly elevated spontaneous sister chromatid exchange rate (90 SCE per cell; more than 10 times what is normally found, which is about 8-10 SCE per cell with BrDU; spontaneous SCE rate (without DNA damaging agent) in the normal population being about 1 per cell); in some persons a minor population of low SCE cells exists, suggesting a recombination event between maternal and paternal alleles (with different mutations), giving rise to a wild type functional gene (called somatic reversion); this allowed to localize the gene in a very elegant strategy.
- Heterozygotes are not detectable by cytogenetic studies.
Other findings

Note: slowing of the cell cycle (lentening of the G1 and S phases); DNA ligase I deficiency (delayed junction of Okazaki fragments).

Genes involved and Proteins

**BLM**

**Location:** 15q26.1

**Protein**

Description: ATP binding, DEAH box, and two putative nuclear localization signals.

Localisation: nuclear.

Function: DNA helicase; probable role in DNA replication and repair.

Homology with the RecQ helicases.

**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.

Somatic: random somatic mutations in random DNA segments appear to randomly cause tumour initiation and/or progression: every cancer type is over-represented in this syndrome, and at a much earlier age than normal.

References


This article should be referenced as such:

Dubowitz syndrome
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)

Published in Atlas Database: February 1998

Online updated version is available from: http://AtlasGeneticsOncology.org/Kprones/DUB10016.html

DOI: 10.4267/2042/37423

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Note: Dubowitz syndrome may be confused with Bloom syndrome; another differential diagnosis is fetal alcohol syndrome.

Inheritance: autosomal recessive; heterogeneity cannot be excluded; less than 150 cases described.

Clinics

Phenotype and clinics
- Phenotypic spectrum variable.
- Growth: from normal to severe retardation; intrauterine growth retardation is frequent; birth weight: 2.3 kg; length: 45 cm; cranial perimeter: 30 cm; delayed bone age.
- Head: microcephaly; high forehead; sparse hair; broad nose; epicanthus; hypertelorism; blepharophimosis; microretrognathia.
- Skin: eczema, a classical sign, may be absent.
- Congenital heart defects in 10%; other malformations: ocular, dental, skeletal, urogenital in male patients; frequent infections.
- Mental retardation in 30-70 % of cases (from normal in 30% to severe retardation in 10%); siezures in 10%
- high-pitched voice; behaviour problems in 40%; most patients are 'hyperactive, shy, like music'.

Neoplastic risk
Haematological malignancies and pancytopenia in 10%, childhood myelodysplasia in particular; lymphomas.

Cytogenetics

Inborn condition
Appears to be normal or near to normal in most cases, although an increased rate of chromosomal breakage has also been described.

References


This article should be referenced as such:
Cancer Prone Disease Section

Mini Review

Fanconi anaemia

Jean-Loup Huret

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

Published in Atlas Database: February 1998

Online updated version is available from: http://AtlasGeneticsOncology.org/Kprones/FA10001.html

DOI: 10.4267/2042/37424

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 1998 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: Fanconi pancytopenia

Inheritance: autosomal recessive; frequency is about 2.5/10^5 newborns.

Clinics

Note: Fanconi anaemia is a chromosome instability syndrome with progressive bone marrow failure and an increased risk of cancers.

Phenotype and clinics

- Growth retardation (70% of cases).
- Skin abnormalities: hyperpigmentation and/or café au lait spots in 80%.
- Skeletal malformations (60%), particularly radius axis defects (absent or hypoplastic thumb or radius...).
- No immune deficiency (in contrast with most other chromosome instability syndromes).
- Progressive bone marrow failure; mean age of onset of anemia: 8 yrs; diagnosis made before onset of haematologic manifestations in only 30%.
- Other: renal anomalies, hypogonadism, mental impairment, heart defects, and perhaps diabetes mellitus, also occur in 10 to 30% of cases.

Neoplastic risk

- Myelodysplasia (MDS) and acute non lymphocytic leukaemia (ANLL): 10% of cases; i.e. a 15000 fold increased risk of MDS and ANLL has been evaluated in FA, and it has been assumed that 'it is reasonable to regard the Fanconi anemia genotype as 'preleukaemia''; mean age at diagnosis: 15 yrs.
- Hepatocarcinoma (androgen-therapy induced) in 10%; mean age at diagnosis: 16 yrs.
- Other cancers in 2-5%; in particular squamous cell carcinoma.

Treatment

Androgens and steroids to improve haematopoietic functions; bone marrow transplantation prevents from terminal pancytopenia, and from ANLL as well.

Prognosis

Mean age at death: 16 years; most patients die from marrow aplasia (haemorrhage, sepsis), and others from malignancies; MDS and ANLL in FA bear a very poor prognosis (median survival of about 6 mths); survival is also poor in the case of a squamous cell carcinoma.

Cytogenetics

Inborn condition

- Spontaneous chromatid/chromosome breaks, triradials, quadriradials.
- Hypersensitivity to the clastogenic effect of DNA cross-linking agents (increased rate of breaks and radial figures); diepoxybutane, mitomycin C, or mechlorethamine hydrochlorid are used for diagnosis.

Cancer cytogenetics

- Various clonal anomalies are found in MDS or ANLL in Fanconi anaemia patients, such as the classical -5/del(5q), and -7/del(7q), found in 10 % of cases; telomeres appear to be non randomly involved in FA's clonal anomalies.

Other findings

Note:

- Slowing of the cell cycle (G2/M transition, with accumulating of cells in G2).
- Impaired oxygen metabolism.
- Defective P53 induction.
Genes involved and Proteins

Complementation groups:
4 well known complementation groups: group A (gene FA1 in 16q24, perhaps another gene 20q13), group B, group C (gene FACC in 9q22), group D (gene FAD in 3p24 has sometimes been located in 11q23); a fifth group, group E, may, per se, be heterogenous; however, the different complementation groups display similar phenotypes, and genes may therefore be functionally related (recently was found that FA1 and FACC form heterodimers).

FA1
Location: 16q24
Protein
Expression: wide.
Localisation: mostly cytoplasmic.
Function: binds to the protein encoded by FACC (see below), the dimer being found in the cytoplasm and the nucleus.
Homology: no known homology.
Mutations
Germlinal: various nucleotide substitutions, deletions, or insertions.

FACC
Location: in 9q22
Protein
Expression: wide.
Localisation: cytoplasmic when unbound.
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 (see above), the dimer being found in the cytoplasm and the nucleus.
Homology: no known homology.
Mutations
Germlinal: nucleotide substitutions.

FAD
Location: 3p24

To be noted
Clinical diagnosis may, in certain cases, be very difficult; cytogenetic ascertainment is then particularly useful; however, cytogenetic diagnosis may also, at times, be very uncertain; this is a great problem when bone marrow engraftment has been decided in a pancytopenic patient: if this patient has FA, bone marrow conditioning must be very mild, as FA cells are very clastogen sensitive. FA patients (i.e. patients with defective alleles) may have, in a percentage of cells, a somatic reversion (by revert mutation towards wild-type gene); such a phenomenon is also known in Bloom syndrome, another chromosome instability syndrome.

References
Alter BP, Potter NU. Chromosome Mutation and neoplasia. J German Ed. AR Liss 1983; pp 43.

This article should be referenced as such:
Instructions to Authors

Manuscripts submitted to the Atlas must be submitted solely to the Atlas. Iconography is most welcome: there is no space restriction.

The Atlas publishes "cards", "deep insights", "case reports", and "educational items".

**Cards** are structured review articles. Detailed instructions for these structured reviews can be found at:
- http://AtlasGeneticsOncology.org/Forms/Gene_Form.html for reviews on genes,
- http://AtlasGeneticsOncology.org/Forms/Leukaemia_Form.html for reviews on leukaemias,
- http://AtlasGeneticsOncology.org/Forms/SolidTumour_Form.html for reviews on solid tumours,

According to the length of the paper, cards are divided into "reviews" (texts exceeding 2000 words), "mini reviews" (between), and "short communications" (texts below 400 words). The latter category may not be accepted for indexing by bibliographic databases.

**Deep Insights** are written as traditional papers, made of paragraphs with headings, at the author's convenience. No length restriction.

**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 http://atlasgeneticsoncology.org/Reports/Case_Report_Submission.html.

**Educational Items** must be didactic, give full information and be accompanied with iconography. Translations into French, German, Italian, and Spanish are welcome.

Subscription: The Atlas is FREE!

Corporate patronage, sponsorship and advertising
Enquiries should be addressed to Editorial@AtlasGeneticsOncology.org.

Rules, Copyright Notice and Disclaimer

**Conflicts of Interest**: Authors must state explicitly whether potential conflicts do or do not exist. Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript. The editor and the editorial board members must disclose any potential conflict.

**Privacy and Confidentiality – Iconography**: Patients have a right to privacy. Identifying details should be omitted. If complete anonymity is difficult to achieve, informed consent should be obtained.

**Property**: As "cards" are to evolve with further improvements and updates from various contributors, the property of the cards belongs to the editor, and modifications will be made without authorization from the previous contributor (who may, nonetheless, be asked for refereeing); contributors are listed in an edit history manner. Authors keep the rights to use further the content of their papers published in the Atlas, provided that the source is cited.

**Copyright**: The information in the Atlas of Genetics and Cytogenetics in Oncology and Haematology is issued for general distribution. All rights are reserved. The information presented is protected under international conventions and under national laws on copyright and neighbouring rights. Commercial use is totally forbidden. Information extracted from the Atlas may be reviewed, reproduced or translated for research or private study but not for sale or for use in conjunction with commercial purposes. Any use of information from the Atlas should be accompanied by an acknowledgment of the Atlas as the source, citing the uniform resource locator (URL) of the article and/or the article reference, according to the Vancouver convention. Reference to any specific commercial products, process, or service by trade name, trademark, manufacturer, or otherwise, does not necessarily constitute or imply its endorsement, recommendation, or favouring. The views and opinions of contributors and authors expressed herein do not necessarily state or reflect those of the Atlas editorial staff or of the web site holder, and shall not be used for advertising or product endorsement purposes. The Atlas does not make any warranty, express or implied, including the warranties of merchantability and fitness for a particular purpose, or assumes any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, and shall not be liable whatsoever for any damages incurred as a result of its use. In particular, information presented in the Atlas is only for research purpose, and shall not be used for diagnosis or treatment purposes. No responsibility is assumed for any injury and/or damage to persons or property for any use or operation of any methods products, instructions or ideas contained in the material herein.

See also: "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication - Updated October 2004": http://www.icmje.org.

http://AtlasGeneticsOncology.org

© ATLAS - ISSN 1768-3262