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, clinical entities in cancer, and cancer-prone diseases. It presents structured review articles (“cards”) on genes, leukaemias, solid tumours, cancer-prone diseases, more traditional review articles on these and also on surrounding topics (“deep insights”), case reports in hematology, and educational items in the various related topics for students in Medicine and in Sciences.

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NUP214 (nucleoporin 214kDa)
Sabine Strehl

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Published in Atlas Database: September 2005

Online updated version: http://AtlasGeneticsOncology.org/Genes/CAN.html
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Identity

Hugo: NUP214
Other names: CAN; CAIN; D9S46E; NUP214 (nuclear pore complex protein 214 kDa)
Location: 9q34.3
Local order: from centromere to telomere: SET, ABL1, NUP214 (alias CAN), NOTCH1 (alias TAN1).

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

Localisation
Nuclear membrane; cytoplasmic face of nucleopore.

Function
Nucleoporins are the main components of the nuclear pore complex (NPC) in eukaryotic cells. The nuclear pore complex is a massive structure that extends across the nuclear envelope, forming a gateway that regulates the flow of macromolecules between the nucleus and the cytoplasm. NUP214 may serve as a docking site in the receptor mediated import of substrates across the NPC, and plays a role in nuclear protein import, mRNA export, and cell cycle progression; interacts with DDX19, NUP88, and XPO1.

Homology
NUP214 is a member of the FG-repeat-containing nucleoporins.

Implicated in

\[ t(6;9)(p23;q34) \rightarrow DEK-NUP214 \]

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' NUP214; chromosome 6 breakpoint clusters in a single intron.
Abnormal Protein
Head to tail DEK/NUP214 fusion protein (the alternative SET/NUP214 is exceptional); almost the entire DEK protein is fused to the C-terminal two-thirds of the NUP214 protein; nuclear localization.

\[ t(9;9)(q34;q34) /AUL \rightarrow \text{SET-NUP214} \]

Note: the only SET-NUP214 positive case described so far had a normal karyotype; on the cytogenetic level it is unclear whether the SET-NUP214 fusion is generated by a t(9;9)(q34;q34) or an interstitial deletion at 9q34; the latter is supported by the centromere-telomere orientation of both genes and their local order: centromere ‘SET - NUP214’ telomere.

Disease
Only one case to date; acute undifferentiated leukemia.

Cytogenetics
May be overlooked.

Hybrid/Mutated Gene
5’ SET - 3’ NUP214

Amplification → NUP214- ABL1

Disease
5-6% of childhood and adult T-ALL.

Prognosis
Aggressive course of disease.

Cytogenetics
Found in T-ALL with various karyotypes.

Hybrid/Mutated Gene
Episomal amplification of the 5’ NUP214 - 3’ ABL1 fusion gene.

Breakpoints

References


References


Gene Section
Mini Review

JAK2 (janus kinase 2)
Sabine Strehl
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Identity
Hugo: JAK2
Location: 9p24

DNA/RNA
Description
25 exons spanning roughly 140 kb of genomic DNA; 5402 bp pre-mRNA; 6 different transcripts, putatively encoding 4 different protein isoforms.

Protein
Description
1132 amino acids; 130.7 kDa; JAK2 contains a central Src homology 2 (SH2) domain, and two C-terminal domains: a tyrosine kinase domain JH1 (also termed PTK or TyrKc domain), and a tyrosine kinase-like domain JH2 (also termed STYKc).

Expression
Wide.

Localisation
Intracellular, possibly membrane associated.

Function
Protein tyrosine kinase of the non-receptor type that associates with the intracellular domains of cytokine receptors: JAK2 is the predominant JAK kinase activated in response to several growth factors and cytokines such as IL-3, GM-CSF and erythropoietin; it has been found to be constitutively associated with the prolactin receptor and is required for responses to gamma interferon.

Homology
JAK2 belongs to the janus kinase subfamily; so far four mammalian JAKs have been identified (JAK1, JAK2, JAK3, and TYK2); human JAK2 is >90% identical to the mouse and the rat JAK2 homologs.

Mutations
Somatic
A high proportion (>50%) of patients with myeloproliferative disorders (MPD; polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis - see below) carry a dominant gain-of-function V617F mutation in the JH2 kinase-like domain of JAK2. This mutation leads to deregulation of the kinase activity, and thus to constitutive tyrosine phosphorylation activity. The incidence of the V617F mutation in different studies ranges from 65-97% in polycythemia vera, from 41-57% in patients with essential thrombocythemia, and from 23-95% in...
patients with idiopathic myelofibrosis. In MPD the mutation is heterozygous in most patients and homozygous only in a minor subset. Mitotic recombination probably causes both 9p LOH and the transition from heterozygosity to homozygosity. The same mutation was also found in roughly 20% of Ph-negative atypical CML, in more than 10% of CML-M7, and 1/5 patients with juvenile myelomonocytic leukemia (JMML). The V617F mutation seems to occur exclusively in hematopoietic malignancies of the myeloid lineage.

**Implicated in**

**t(8;9)(p21-22;p24)/acute leukaemias → PCM1-JAK2**

**Disease**
Myeloid and lymphoid malignancies; predominantly atypical CML, but also found in chronic eosinophilic leukemia (CEL), (secondary) AML, and MDS/MPD; thirteen cases described to date, all male, except for one childhood female case with erythroid leukemia with multiple bone tumors.

**Prognosis**
Highly variable; allogeneic stem cell transplantation may be the only curative treatment.

**Hybrid/Mutated Gene**
5’ PCM1 - 3’ JAK2; only in some cases the reciprocal 5’ JAK2 - 3’ PCM1 is present.

**Abnormal Protein**
Almost the entire PCM1 protein containing multiple coiled-coil domains is fused to the tyrosine kinase C-terminal domains (JH2 and JH1) of JAK2.

**Oncogenesis**
Dimerization or oligomerization of the PCM1-JAK2 chimera through one or more of the coiled-coil motifs of PCM1 probably results in the constitutive activation of the tyrosine kinase domain of JAK2.

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

**Disease**
Myeloid and lymphoid leukemias; only three cases described to date; one case each: childhood T-ALL, pre B-ALL, atypical CML.

**Prognosis**
Unknown.

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

**Abnormal Protein**
In the atypical CML the N-terminal HLH of ETV6 is fused to the tyrosine kinase C-terminal domains (JH2 and JH1) of JAK2; in the B-ALL the same ETV6 domain is fused to part of the JH2 and the complete JH1 domain, and in the T-ALL case to the JH1 domain.

**Oncogenesis**
It may be speculated that the HLH domain of ETV6 provides a dimerization interface to the kinase domain of JAK2, which activates JAK2; ETV6-JAK2 transgenic mice - generated using a T-ALL specific fusion construct - develop fatal CD8+ acute T-cell leukemia.

**t(9;22)(p24;q11.2)/MPD → JAK2-BCR**

**Disease**
Atypical CML; only one case described to date.

**Hybrid/Mutated Gene**
5’ BCR - 3’ JAK2; absence of the reciprocal 5’ JAK2 - 3’ BCR.

**Abnormal Protein**
The N-terminal coiled-coil domain of BCR is fused to the JH1 tyrosine kinase C-terminal domain of JAK2.

**Oncogenesis**
 Constitutive activation of the tyrosine kinase domain of JAK2 mediated through oligomerization through the coiled-coil domain of BCR.

**Polycythemia vera/Essential thrombocythemia/Idiopathic thrombocythemia/Idiopathic myelofibrosis**

**Note:** the V617F mutation in JAK2 could form the basis for a new molecular classification of myeloproliferative disorders.

**Disease**
Chronic myeloproliferative syndromes.

**Oncogenesis**
A significant percentage of patients with myeloproliferative disorders carries a dominant gain of function V617F mutation in JAK2; this mutation seems to lead to deregulation of the kinase activity of JAK2, and thus to constitutive tyrosine phosphorylation activity, providing hematopoietic cells with a proliferative and survival advantage.
JAK2 (janus kinase 2)

References


disorders and acute erythroid leukemia with t(8;9) translocation. Leukemia 2005;19(9):1692-1696.


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

ZNF217 (zinc finger protein 217)
Paul Yaswen, Colin Collins

Life Sciences Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Bldg 977-225A, Berkeley, CA 94720-8174, USA

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Identity
Hugo: ZNF217
Other names: 13009; FLJ14031; ZABC1
Location: 20q13.2

DNA/RNA
Description
5 exons.

Transcription
Exon 4 encodes a TGA termination codon and is alternatively processed.

Pseudogene
None.

Genomic organization of ZNF217. (A) The genomic organization of the five exons with encoded initiation and termination codons that make up ZNF217. Hatched boxes represent known 59- and 39-untranslated regions (UTR) in the cDNA. The sizes of exons and introns appear below and above the map, respectively. (B) The map of the 5632-bp ZNF217 cDNA. Vertical bars represent exon boundaries. The relative positions of the predicted eight C2H2 Kruppel-like zinc finger motifs are indicated by white circles. The position of the proline-rich putative transcription activator domain is shown as a hatched oval. AUUUA motifs are indicated in the 39-untranslated region. The relative locations of three ESTs are shown in boxes.
Protein

Description
Full-length ZNF217 cDNAs encode two open reading frames of 1,062 and 1,108 amino acids, due to alternative splicing of exon 4. Each predicted protein has eight C2H2 zinc fingers and a proline-rich domain. Sequence analysis of ZNF217 indicates a strong resemblance to members of the Kruppel-like family of zinc finger proteins. The eight zinc finger domains in ZNF217 are interspersed throughout the ZNF217 sequence and their pattern does not appear to fall into one of the three classes of C2H2 zinc finger proteins; triple-C2H2, multiple-adjacent, and separated-paired fingers. The sixth and seventh zinc fingers in ZNF217 are separated by the conserved linker sequence, TGEKP, reported to bind DNA with high affinity. Database analysis indicates that this paired zinc finger region aligns with those in several members of the Delta-EF1/ZFH-1 family of two-handed zinc-finger homeodomain proteins, including Smad-Interacting Protein 1 (SIP-1).

Expression
ZNF217 is expressed at low levels in normal tissues.

Localisation
Nuclear

Function
ZNF217 protein localizes to the nucleus and co-immunoprecipitates with complexes containing the transcriptional corepressors CoREST and CtBP, histone deacetylases HDAC1 and HDAC2, and histone methyltransferases G9a and Ei-HMTase1. This strongly suggests that ZNF217 may function as part of a transcriptional repressor complex.

Implicated in
The findings that ZNF217 can immortalize human mammary epithelial cells, and that its amplification is associated with poor prognosis, suggest that it may play roles in both early and late stage breast cancer. ZNF217 can attenuate apoptotic signals resulting from telomere dysfunction as well as from doxorubicin-induced DNA damage, while silencing ZNF217 with siRNA restores sensitivity to doxorubicin. Moreover, elevated ZNF217 leads to increased phosphorylation of Akt, whereas inhibition of the phosphatidylinositol 3 kinase pathway and Akt phosphorylation decreases ZNF217 protein levels and increases sensitivity to doxorubicin. These results suggest that ZNF217 may promote neoplastic transformation by increasing cell survival during telomeric crisis, and may promote later stages of malignancy by increasing cell survival during chemotherapy.

References


This article should be referenced as such:
t(2;3)(p15-23;q26-27)

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Identity

Note: There are 2 subtypes of the t(2p;3q): in one type the breakpoint on chromosome 2 is assigned to bands 2p21-23, whereas the breakpoint for the other type of breakpoint is localized at 2p15-21.

Clinics and pathology

Disease

Myeloid malignancies: myelodysplastic syndrome (MDS) in 1/4 of cases, with various FAB diagnoses (refractory anaemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMML)), acute non lymphocytic leukaemia (ANLL) in 60% of cases (M2-ANLL in 1/4 of all cases), blast crisis of a chronic myelogenous leukaemia (BC-CML) in about 10% of cases.

Partial GTG (Marian Stevens-Kroef, left) and RFA (Anne Hagemeijer, right) banded karyotypes of t(2;3)(p15-23;q26-27) with the distal (A) and proximal (B) breakpoint on chromosome 2.
**Etiology**

1/4 of cases were therapy related leukemias, and 10% were BC-CML cases.

**Epidemiology**

At least 50 cases described; sex ratio: 1.33 M/F; median age around 50 years, most patients being between 30 and 70 year old (range 3-80 years).

**Cytology**

High platelet count, dysmegakaryopoiesis, and multilineage dysplasia in 80 to 90% of cases.

**Prognosis**

Median survival 12 months (range 1-53 months), with a few patients surviving with bone marrow transplantation.

**Cytogenetics**

Note: Heterogeneous breakpoints by cytogenetic and FISH analysis; FISH mapping of 2p breakpoints was very heterogeneous ranging from p14 or p15 to p23; FISH mapping of the 3q breakpoint was within the EVII-MDS region (between RP11-694D5 (centromeric) and RP11-362K14 (telomeric) in the great majority of cases.

**Additional anomalies**

Sole anomaly in 40%, associated with -7 in 30%, with del(5q) in 15%, with del(7q) in 10%, with t(9;22)(q34;q11) in 10%, and with a complex karyotype in 20% of cases.

**Genes involved and Proteins**

Note: Molecular analysis has been performed in only a very few cases. In most of these, ectopic expression of EVII was demonstrated, but rare cases seem not to involve this gene. Therefore, characteristics of EVII involvement (high platelet count, multilineage dysplasia, monosomy 7, prior history of carcinogen exposure and a poor prognosis) may not be present in further cases with apparently the same breakpoints. The gene(s) involved in chromosome 2 is/are unknown.

**EVII**

**Location:** 3q26

**Note:** There is a direct correlation between mapping of the 3q breakpoint in the above given EVII-MDS region and EVII ectopic expression by RT-PCR. Rare case with 3q break outside this interval failed to show ectopic expression of EVII.

**DNA / RNA**

EVII contains 12 exons.

**Protein**

EVII may play an important role in organogenesis, cell migration, cell growth, and differentiation.

**References**


Yunis JJ. Recurrent chromosomal defects are found in most patients with acute nonlymphocytic leukemia. Cancer Genet Cytogenet 1984;1:125-137.


Leukaemia Section
Mini Review

\textbf{t(2;11)(q11;q23)}
Anne RM von Bergh

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**Clinics and pathology**

**Disease**
Acute lymphocytic leukemia (ALL) with proB phenotype.

**Epidemiology**
Three cases reported to date, two infants and one two-year-old child.

**Prognosis**
Both cases of infant ALL showed a poor survival, 2 and 9 months respectively. The third case, a two-year-old child, achieved complete remission.

**Cytogenetics**

**Cytogenetics molecular**
The three reported cases carried different rearrangements involving chromosomes 2 and 11: 
t(2;11)(p15;p14), t(2;11)(q11;q23) and ins(11;2)(q23;q11.2q11.2).

**Probes**
LAF4 specific PACs: RP6-44B23 and RP6-226I23.

**Genes involved and Proteins**

**MLL**

\begin{itemize}
  \item \textbf{Location:} 11q23
  \item \textbf{DNA / RNA:} 13-15 kb mRNA.
  \item \textbf{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.
\end{itemize}

**LAF4**

\begin{itemize}
  \item \textbf{Location:} 2q11-q12
  \item \textbf{Note:} AF4 and AF5q31, also known as MLL fusion partners, belong to the same gene family.
  \item \textbf{DNA / RNA:} 22 exons, transcript length: 3855 bp.
  \item \textbf{Protein:} LAF4 protein (Lymphoid nuclear protein related to AF4) 1226 amino acids; 133734 Da.
\end{itemize}

Schematic representation of MLL, LAF4, and the putative MLL-LAF4 fusion protein. MT, methyltransferase domain; TRX, Drosophila trithorax homology; NHD, N-terminal homology domain; TAD, transactivation domain; NLS, nuclear localization sequence; CHD, C-terminal homology domain.
Results of the chromosomal anomaly

Hybrid gene
Transcript
5’ MLL - 3’ LAF4

Fusion protein
Description
The MLL-LAF4 fusion protein includes the transactivation domain of LAF4 that is part of the AF4/LAF4/FMR2 homology domain.

References
Ma C, Staudt LM. LAF-4 encodes a lymphoid nuclear protein with transactivation potential that is homologous to AF-4, the gene fused to MLL in i(4;11) leukemias. Blood 1996;87:734-745.

This article should be referenced as such:
t(3;7)(q26;q21)
Clelia Tiziana Storlazzi, Francesco Albano

Department of Genetics and Microbiology, University of Bari, Via Amendola 165/A, 70126 Bari, Italy

Identity

Partial karyotype showing an unbalanced t(3;7)(q26;q21).

Clinics and pathology

Note: This translocation has been observed in myeloid leukemia [one case of acute myeloid leukemia (AML), subtype M4, and two cases of chronic myeloid leukemia in blast crisis (CML-BC)].

Disease
Blast crisis chronic myelogenous leukemia (myeloid-myoeloid/NK phenotype).

Phenotype / cell stem origin
Myeloid leukemia.

Prognosis
Poor.

Disease
AML M4.

Phenotype / cell stem origin
Acute myeloid leukemia.

Prognosis
Poor.

Cytogenetics

Cytogenetics morphological

\( t(3;7)(q26;q21) \) in BC-CML; -7,+der(7)t(3;7)(q26;q21) in AML M4.

Probes
RP11-33A1 (EVI1) RP11-332M5 (CDK6).

Additional anomalies
Sole anomaly in AML; Ph chromosome in BC-CML patients.

Variants
No variants described.

Genes involved and Proteins

EVI1 (ecotropic viral integration site 1) (alias PRDM3)

Location: 3q26.2

Note: EVI1 is expressed at very low levels in normal peripheral blood and bone marrow. The gene is overexpressed in myeloid leukemias and myelodysplastic syndromes as a result of chromosomal rearrangements at either the 5' region of the gene in t(3;3)(q21;q26) or at the 3' region in inv(3)(q21q26) by juxtaposition of the gene to putative enhancer elements of the Ribophorin I gene in 3q21. High expression of EVI1 can also occur in the t(3;21)(q26;q22) as part of the fusion gene AML1 / MDS1 / EVI1 in CML-BC, or MDS or as part of the fusion gene ETV6 / MDS1 / EVI1 in AML with t(3;12) translocation. EVI1 is also involved in other translocations such as t(2;3)(p13;q26), t(2;3)(q23;q26), t(3;17)(q26;q22) and t(3;13)(q26;q13-14). Other studies have reported abnormal expression of EVI1 in MDS and AML without 3q26 structural abnormalities, suggesting that inappropriate activation of this gene occurs through various mechanisms.

DNA / RNA
16 exons spanning 64.2 kb. Transcriptional orientation is from telomere to centromere. 6 splicing variants.

Protein
1051 amino acids; 118335 Da. Nuclear location, contains 10 C2H2-type zinc fingers.
FISH cohybridization between clones identifying breakpoints on chromosome 3 (RP11-33A1) and 7 (RP11-332M5) in a case of BC-CML with a t(3;7)(q21;q26).

**CDK6 (cyclin-dependent kinase 6) (alias PLSTIRE)**

**Location:** 7q21.2  
**DNA / RNA**  
7 exons spanning 229 kb. Transcriptional orientation is from telomere to centromere.  
**Protein**  
326 amino acids; 36938 Da. It belongs to the Ser/Thr protein kinase family, CDC2 /CDKX subfamily. It is probably involved in the control of the cell cycle. Interacts with D-type G1 cyclins.

**Results of the chromosomal anomaly**

**Hybrid gene**  
**Note:** overexpression of EVI1 in bone marrow; no detected CDK6/EVI1 fusion gene in any of the myeloid leukemia cases analyzed.

**References**


This article should be referenced as such:  
t(4;12)(p16;p13)
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Clinics and pathology

Disease
Peripheral T-cell lymphoma.

Epidemiology
Only one case to date, a 63 year old female patient.

Prognosis
No data.

Cytogenetics

Additional anomalies
Were found.

Genes involved and Proteins

FGFR 3
Location: 4p16.3
Protein
115 kDa; contains, from N-term to C- term: an extracellular domain with a signal sequence and 3 Ig-like loops, a transmembrane domain, and an intracellular domain with 2 tyrosine kinase domains. FGFR3 is a fibroblast growth factor receptor with tyrosine kinase activity; binding of ligand (FGF) induces receptor dimerization, autophosphorylation and signal transduction.

ETV6
Location: 12p13
Protein
53 and 57 kDa; contains, from N-term to C- term: an helix -loop-helix (HLH) domain (or 'sterile alpha domain' SAM) responsible of r dimerization, and a sequence specific DNA-binding domain (ETS domain); binds to 5' CCGGAAGT 3'; ETV6 is a member of the ETS family of transcription factors; transcriptional repressor.

Results of the chromosom al anomaly

Hybrid gene
Description
5' ETV6 - 3' FGFR3; splicing variants (1618 and 1767 bp); the 1767 bp variant is an in frame fusion of ETV6 exon 5 to FGFR3 exon 10; both breakpoints are within exons; no reciprocal transcript.

Fusion protein
Description
Contains, from N-term to C- term, the HLH domain of ETV6 fused to the tyrosine kinase domains of FGFR3.

References

Leukaemia Section
Short Communication

**t(7;17)(p15;q23)**

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**Clinics and pathology**

**Disease**

Chronic myelogenous leukemia (CML) in accelerated phase (AP-CML).

**Epidemiology**

Only one case to date, a female patient, aged 50 at the time of the AP-CML.

**Prognosis**

Chronic phase of CML lasted 2 years before progression into an accelerated phase accompanied with the appearance of the t(7;17); the patient died in blast crisis of the CML 13 months after the AP-CML, 3 years after initial diagnosis of CML.

**Cytogenetics**

**Cytogenetics morphological**

A t(9;22)(q34;q11) was, indeed, present.

**Cytogenetics molecular**

Cryptic translocation; recognized by multicolor FISH plus locus-specific FISH.

**Genes involved and Proteins**

**HOXA9**

**Location:** 7p15

**Protein**

DNA binding domain (homeobox) in C-term (amino acids 206 to 265); sequence specific transcription factor; Hox proteins are in linear arrangement correlated with the genes expression during embryogenesis; regulate cell proliferation, cell migration, and segmental embryonic patterning.

**MSI2**

**Location:** 17q23.2

**DNA / RNA**

At least 15 exons; various splicing.

**Protein**

Possesses 2 RNA recognition motifs; likely to be a RNA binding protein; may play a role in RNA metabolism in the cytoplasm; the mouse homolog is ubiquitous, and particularly active in the brain development.

**Results of the chromosomal anomaly**

**Hybrid gene**

**Description**

5' MSI2 - 3' HOXA9; in frame fusion of MSI2 exon 9 to the intermediate alternatively spliced exon 1b (IME) of HOXA9.

**Fusion protein**

**Description**

Contains, from N-term to C-term, the 2 RNA recognition motifs of MSI2 and the the IME and the homeobox domain of HOXA9.

**References**


This article should be referenced as such: Huret JL. t(7;17)(p15;q23). Atlas Genet Cytogenet Oncol Haematol. 2006;10(1):17-18.
Leukaemia Section
Short Communication

\[ t(7;17)(q32-34;q23) \]
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Clinics and pathology

Disease
Chronic myelogenous leukemia (CML) in accelerated phase (AP-CML).

Epidemiology
Only one case to date, a female patient, aged 40 at the time of the AP-CML.

Prognosis
Chronic phase of CML lasted 2 years before progression into an accelerated phase accompanied with the appearance of the \( t(7;17) \); 2 months later, a blast crisis occurred, and the patient died 9 months after the AP-CML, 33 months after initial diagnosis of CML.

Cytogenetics

Cytogenetics morphological
A \( t(9;22)(q34;q11) \) was, indeed, present.

Cytogenetics molecular
Cryptic translocation; recognized by multicolor FISH plus locus-specific FISH.

Genes involved and Proteins

Note: The gene involved on chromosome 7 is undefined, due to a lack of material for further analysis, but it seems to be a gene of the plexin family, with, perhaps, a sema domain, a plexin repeat, and an immunoglobulin-like plexin transcription factor domain.

\( MSI2 \)
Location: 17q23.2

DNA / RNA
At least 15 exons; various splicing.

Protein
Possesses 2 RNA recognition motifs; likely to be a RNA binding protein; may play a role in RNA metabolism in the cytoplasm; the mouse homolog is ubiquitous, and particularly active in the brain development.

References


This article should be referenced as such:
Leukaemia Section

Mini Review

t(9;9)(q34;q34)

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Clinics and pathology

Disease

Acute undifferentiated leukemia (AUL).

Epidemiology

Only one case described so far.

Cytogenetics

Note: the only SET-NUP214 positive case described so far had a normal karyotype; on the cytogenetic level it is unclear if the SET-NUP214 fusion is generated by a t(9;9)(q34;q34) or an interstitial deletion at 9q34; the latter is supported by the centromere-telomere orientation of both genes and their local order: centromere-SET-NUP214-telomere.

Cytogenetics morphological

The single case described so far had a normal karyotype; may be overlooked.

Genes involved and Proteins

SET

Location: 9q34

DNA / RNA

8 exons spanning 6,81 kb of genomic DNA; 2559 bp mRNA.

Protein

Two isoforms; isoform 1 (TAF1 alpha) 290 amino acids, 33.5 kDa; isoform 2 (TAF1 beta) - 277 amino acids, 23.1 kDa; DNA associated, transcription factor; multitalking protein, involved in apoptosis, transcription, nucleosome assembly and histone binding; cytoplasmic and nuclear; in the cytoplasm, found both in the cytosol and associated with the endoplasmic reticulum.

NUP214

Location: 9q34

DNA / RNA

36 exons encompassing about 108 kb of genomic DNA; 6.6 kb mRNA.

Protein

2090 amino acids, 213.8 kDa; forms homodimers, contains two leucine zipper dimerization domains, and FG repeats at the C-terminus, which are homologous to those observed in other members of the nucleoporin family; expressed in thymus, spleen, bone marrow, kidney, brain and testis, but hardly in all other tissues or in whole embryos during development; may serve as a docking site in the receptor-mediated import of substrates across the nuclear pore complex (NPC); intracellular localization, cytoplasmic face of the NPC.

Results of the chromosomal anomaly

Hybrid gene

Transcript

5' SET - 3' NUP214

Fusion protein

Description

The SET-NUP214 fusion protein consists of almost the whole SET protein fused to the C-terminus of NUP214; 155 kDa.

Oncogenesis

SET-NUP214 leads to disorganization of nuclear export.
References


t(9;11)(q34;q23) AF9q34/MLL

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Identity

Note: Not to be confused with the t(9;11)(q34;q23), involving MLL and FBP17.

Clinics and pathology

Disease

De novo AML M5.

Epidemiology

Only one case to date, a 62-year-old male patient.

Clinics

The patient presented with multi-organ failure due to leukostasis and infection. WBC was 248 x 10^9/L.

Prognosis

Patient died within a few months after diagnosis.

Cytogenetics

Additional anomalies

+8 and +13 in 40% of metaphases.

Genes involved and Proteins

MLL

Location: 11q23
DNA / RNA
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.

AF9q34

Location: 9q34, centromeric of FBP17 and ABL.
DNA / RNA
14 exons stretched over an area of about 84 kb, 5192 bp mRNA.

Protein

967 amino acids; contains a GAP related domain (GRD), an 'FLR'-motif, a Pleckstrin homology (PH) domain and a calcium/phospho-lipid-binding C2/CALB domain.

Results of the chromosomal anomaly

Hybrid gene

Transcript

5' MLL - 3' AF9q34.

Fusion protein

Description

MLL/AF9q34 contains the AT-hook, DNA-Methyltransferase, Zinc-Fingers domains of MLL and the entire GAP related domain (GRD) and the C2/CALB domain of AF9q34.
References


This article should be referenced as such:
von Bergh ARM. t(9;11)(q34;q23) AF9q34/MLL. Atlas Genet Cytogenet Oncol Haematol. 2006;10(1):22-23.
t(11;12)(q23;q13) MLL/CIP29

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Clinics and pathology

Disease
M4 acute non lymphocytic leukaemia (ANLL).

Epidemiology
Only 1 case to date: a 7 months old boy.

Prognosis
No data.

Cytogenetics

Additional anomalies
Sole anomaly in this case.

Genes involved and Proteins

MLL
Location: 11q23
DNA / RNA
36 exons, spans over 100 kb, ORF 12 kb.
Protein
3969 amino acids; 431 kDa; contains two DNA binding motifs (a AT hook and a DNA methyltransferase homology motif), trithorax homology domains, zinc finger domains with features of PHD fingers and the C-terminal SET domain.

CIP29
Location: 12q13
Protein
210 amino acids, 29 kDa; contains from N term to C term a SAP domain and 2 nuclear localization domains.

Results of the chromosomal anomaly

Hybrid gene
Description
5’ MLL - 3’ CIP29 including the 9 first exons of MLL, and nearly the entire CIP29

Fusion protein
Description
The fusion protein includes from N term to C term the AT hooks and the methyltransferase domain of MLL and the SAP domain and the C term nuclear localization domains of CIP29.

References


This article should be referenced as such:
Leukaemia Section

Mini Review

t(11;17)(q23;q12-21) MLL/AF17

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Identity

Note: Not to be confused with the t(11;17)(q23;q12-21) involving MLL and LASP1 or the t(11;17)(q23;q12-21) involving MLL and ACACA.

Disease

Acute myeloid leukemia (AML).

Epidemiology

Not sufficient cases to date.

Clubs and pathology

Cytogenetics

Note: so far three MLL fusion partners, namely LASP1, AF17 (alias MLLT6), and ACACA have been identified in 17q12-21; these translocations cannot be distinguished cytogenetically and the accurate detection of the specific fusion gene requires RT-PCR or refined FISH analysis.

Cytogenetics molecular

Chromosomes (arrows on the figure below).

Probes


Additional anomalies

+8.

Genes involved and Proteins

MLL

Location: 11q23

DNA / RNA

37 exons, spanning over 100 kb; transcription in a centromeric to telomeric direction; 13 -15 kb mRNA; coding sequence 11.9 kb.

Protein

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

MLLT6 (alias AF17)

Location: 17q12

Note: previously LASP1 and AF17 (alias MLLT6) were mapped to 17q21, but according to the most recent genome assembly built by the Genome Bioinformatics Group of the University of California Santa Cruz and recent FISH data both genes are localized in 17q12 and proximal to RARA.
FISH using a combination of the MLL-specific PACs 217a21 and 167k13 (green signals) and the AF17-specific BAC RP11-25H10 (red signals) results in two fusion signals on the der(11) and the der(17).

Schematic representation of MLL, AF17 (alias MLLT6), and the putative MLL-AF17 fusion protein. MT, methyltransferase domain; Zn finger, Zinc finger domain; SET-domain; PHD, Zinc finger PHD-type; OM, octapeptide motif; LZ, leucine-zipper dimerization motif.

DNA / RNA
Encompasses 19.97 kb of genomic DNA; 4914 bp mRNA; 20 exons, 3282 bp coding sequence.

Protein
1023 amino acids, 112 kDa; MLLT6 (alias AF17), MLLT10 (alias AF10), and BRPF1 (alias BR140) belong to a small evolutionary highly conserved family of putative nuclear transcription factors, which contain amino-terminal PHD fingers, a highly conserved octapeptide, and a classical leucine zipper dimerization motif; nuclear localization.

Results of the chromosomal anomaly

Hybrid gene

Transcript
5' MLL - 3' AF17

Fusion protein

Description
The AT-hook DNA-binding domain and the methyltransferase motif including the CXXC zinc-finger (Zn) domain of MLL are fused to the highly conserved octapeptide (OM) and the leucine-zipper (LZ) dimerization motif of AF17 (alias MLLT6).

References


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

**t(11;17)(q23;q12-21) MLL/LASP1**

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**Identity**

\[ t(11;17)(q23;q12-21) \]

\[ t(11;17q23q12-21) \] G-banding - Courtesy Melanie Zenger and Claudia Haferlach.

**Clinics and pathology**

**Disease**

Infant acute myeloid leukemia AML-M4

**Epidemiology**

Only one case described so far.

**Prognosis**

Insufficient data; of note: the only patient described, remains in complete remission >8 years.

**Cytogenetics**

**Note:** so far three MLL fusion partners, namely LASP1 (in the t(11;17) herein described), MLLT6 (alias AF17) (in another t(11;17)(q23;q12-21) ), and ACACA (also in another t(11;17)(q23;q12-21) ) have been identified in 17q12-21; these translocations cannot be distinguished cytogenetically and the accurate detection of the specific fusion gene requires RT-PCR or refined FISH analysis.

**Cytogenetics morphological**

Sole abnormality.

**Genes involved and Proteins**

**MLL**

**Location:** 11q23

**DNA / RNA**

37 exons, spanning over 100 kb; transcription in a centromeric to telomeric direction; 13 and 15 kb mRNA; coding sequence: 11.9 kb.

**Protein**

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

**LASP1**

**Location:** 17q12

**Note:** previously LASP1 and MLLT6 (alias AF17) were mapped to 17q21, but according to the most recent genome assembly built and recent FISH data both genes are localized in 17q12 and proximal to RARA.

**DNA / RNA**

7 exons spanning about 50 kb of genomic DNA; 3845 bp mRNA, 783 bp coding sequence; ubiquitous expression.

**Protein**

LASP1 encodes a member of a LIM protein subfamily; contains a LIM motif, two actin-binding domains, and an SH3 domain; cytoplasmic localization.
Results of the chromosomal anomaly

Hybrid gene

Transcript

5’ MLL - 3’ LASP1; also the reciprocal 5’ LASP1 - 3’ MLL is present.

Fusion protein

Description

The C-terminal SH3 domain of LASP1 is fused to the N-terminal portion of MLL retaining the AT-hook DNA-binding domain and the DNA methyltransferase motif (MT).

References


This article should be referenced as such:

Leukaemia Section
Short Communication

\( t(12;14)(p13;q32) \)
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**Clinics and pathology**

*Disease*
Acute lymphoblastic leukemia.

*Phenotype / cell stem origin*
Pre B ALL.

*Epidemiology*
Only one case to date; no age nor gender data.

*Prognosis*
No data.

**Cytogenetics**

*Cytogenetics molecular*
Cryptic translocation; recognized by multicolor FISH plus locus-specific FISH.

*Additional anomalies*
Hyperploidy (57 chromosomes).

**Genes involved and Proteins**

*ETV6*

*Location:* 12p13

*Protein*
53 and 57 kDa; contains, from N-term to C-term, an helix-loop-helix (HLH) domain (or 'sterile alpha domain' SAM) responsible of dimerization, and a sequence specific DNA-binding domain (ETS domain); binds to 5’ CCGGAAGT 3’; ETV6 is a member of the ETS family of transcription factors; transcriptional repressor.

*IGH*

*Location:* 14q32

**References**


This article should be referenced as such:
Kidney: inv(X)(p11.2;q12) in renal cell carcinoma

Pedram Argani, Marc Ladanyi

Department of Pathology, room S-801, MSKCC, 1275 York Avenue, New York, NY 10021, USA (PA); Department of Surgical Pathology, The Johns Hopkins Hospital, Weinberg Building, Room 2242, 401 North Broadway, Baltimore, MD 21231-2410, USA (ML)

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Identity

Other names: NONO-TFE3 renal cell carcinoma

Classification

This renal cell carcinoma, of which there is a single reported case, belongs to the family of Xp11 translocation renal carcinomas.

Clinics and pathology

Etiology

Unclear.

Epidemiology

Single case report in a 39-year-old male.

Pathology

The tumor was described as a papillary renal cell carcinoma. The UOK109 cell line was derived from this neoplasm.

Treatment

Surgical excision.

Prognosis

Unknown.

Cytogenetics

Cytogenetics morphological
inv(X)(p11.2;q12)

Genes involved and Proteins

TFE3
Location: Xp11.2

DNA/RNA

The TFE3 gene includes a 5’ untranslated region, 8 exons, and a 3’ untranslated region.

Protein

TFE3 is a transcription factor with a basic helix-loop-helix DNA binding domain and a leucine zipper dimerization domain. TFE3 contains a nuclear localization signal, encoded at the junction of exons 5 and 6, which is retained within all known TFE3 fusion proteins. TFE3 protein is 575 amino acids, and is ubiquitously expressed. TFE3, TFEB, TFEC and Mitf comprise the members of the microphthalmia transcription factor subfamily, which have homologous DNA binding domains and in fact bind to a common DNA sequence. These four transcription factors may homo- or heterodimerize to bind DNA, and they may have functional overlap.

p54nrb/NONO

Location: Xq12

Protein

p54nrb/NONO is a 471 amino acid protein with several distinctive domains. From N-terminus to C-terminus, it has:
1) an N-terminal basic region composed entirely of Proline, Glutamine, and Histidine,
2) a pair of RNA recognition motifs,
3) a helix-turn helix domain followed by a series of charged amino acids that likely forms a DNA-binding unit,
4) a short C-terminal Proline-rich region.
PSF and p54nrb/NonO are highly homologous and related proteins. p54nrb/NONO has a region of 320 amino acids with a 71% identity and a 7% similarity to a 320 amino acid region within PSF. Both proteins have both DNA and RNA binding domains, which
underlies their multifunctionality. Indeed, these proteins have been implicated in both transcriptional activation and splicing. Both proteins are known to bind to the DNA binding domains of nuclear hormone receptors (such as the thyroid hormone receptor and the retinoid X receptor), and modulate transcriptional activation. These proteins bind to each other, select the same optimal RNA sequence from RNA pools, and have been associated with spliceosomes. Both have been shown to bind to the C-terminal domain of RNA polymerase II, where they may couple pre-mRNA splicing and RNA processing. PSF and NonO enhance Topoisomerase I cleavage of DNA, and induce its jumping to other DNA helices after cleavage. Finally, both have been shown to bind and retain defective and hyperedited mRNAs within the nucleus, preventing translation of mutated proteins.

### Result of the chromosomal anomaly

**Hybride Gene**

**Description**

5' p54nrb/NONO - 3' TFE3

**Fusion protein**

**Description**

The inv (X)(p11.2;q12) results in fusion of virtually the entire sequence of NONO/p54nrb with the C-terminal portion of the TFE transcription factor that contains the basic helix-loop-helix (bHLH) DNA binding domain and Leucine Zipper domain.

### References


This article should be referenced as such:

Solid Tumour Section
Short Communication

Soft tissue tumors: Malignant myoepithelioma

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Clinics and pathology

Disease

In the recent WHO classification of tumors of soft tissue and bone, myoepithelioma is considered to be part of a spectrum that also embraces mixed tumor and parachordoma.

Soft tissue myoepithelioma is a rare tumor displaying myoepithelial elements within a hyalinized to chondromyxoid stroma and lacking obvious ductal differentiation. The histogenesis is unclear and most are benign, but some behave in a malignant fashion.

Cytogenetics

Note: To date there are no cytogenetic data on soft tissue myoepithelioma as such except for one case: the stemline is described as 82,XXYY,+Y,-1,add(1)(p13),-3,del(3)(p21),-4,del(4)(q27q34),-6,6,add(7)(p21), der(9)t(1;9)(q25;p22)
or (q31; p23)x2,+der(9)(9,9)(p13;q22).-10,-11,-13,-14,-18,-21,-22[4] and the sideline as 86,idem,+7,+8,+9,-der(9)(9,9),+15.i(20)(q10),+21,add(22)(p1)[4].

This case shares some cytogenetic aberrations described in pleiomorphic adenomas of the salivary gland and basal cell (myoepithelial) adenocarcinoma especially rearrangements of chromosome 1 and 9 and some numerical chromosomal aberrations mentioned in chordomas, especially losses of chromosomes 3, 4, and to all lesser extent, 10 and 13.

These cytogenetic aberrations seem unrelated to previously reported chromosome changes usually seen in closely related entities like parachordoma and intramuscular mixed tumor in which cases mostly loss of material from the short arm of chromosome 17 was detected. It might be that soft tissue myoepithelioma is a distinct entity with some resemblance to (para-)chordoma on the one hand and myoepithelioma on the other. It was recently observed that benign human myoepithelial tumors of diverse sources exhibit common mRNA expression profiles indicative of a tumor-suppressor phenotype.

References


This article should be referenced as such:
Kidney: t(10;17) in clear cell sarcoma of the kidney

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Identity

Other names: bone metastasizing renal tumor of childhood

Clinics and pathology

Disease
Clear cell sarcoma of the kidney (CCSK) is a malignant renal tumor of childhood with a propensity to metastasize to bone and other organs. This tumor may also recur many years after its initial diagnosis. The average age at diagnosis is 2-4 years. CCSK is unrelated to the clear cell sarcoma of the soft tissue, also known as malignant melanoma of soft parts. Extrarenal tumors histologically identical to CCSK have been reported in rare instances. This tumor may be confused with other pediatric renal tumors including blastema-predominant Wilms' tumor, malignant rhabdoid tumor, and cellular mesoblastic nephroma.

Phenotype stem cell origin
Undifferentiated mesenchyme.

Embryonic origin
Mesoderm

Etiology
The tumor is composed of undifferentiated cells as illustrated by its relative lack of immunohistochemical reactivity. Its gene expression profile with a lack of WT-1 mRNA transcripts and elevated levels of IGF-2 mRNA further suggest that the tumor arises from an undifferentiated renal stem cell. Most studies fail to implicate the involvement of the p53 tumor suppressor gene.

Epidemiology
CCSK comprises 5 percent of primary pediatric renal tumors with the peak incidence in the second year of life; however, patients' ages have ranged from 2 months to 54 years. Adult cases are extraordinarily rare. CCSK does not appear to be associated with genetic syndromes like Wilms' tumor (i.e. WAGR, Beckwith-Wiedemann, and Denys-Drash syndromes). Males appear to be more commonly affected than females. The National Wilms' Tumor Study (NWTS) has classified CCSK as one of the most common of the prognostically unfavorable histology tumors (others being anaplastic Wilms' tumor and malignant rhabdoid tumor of the kidney).

Clinics
The usual presentation of CCSK is a child with a flank mass with or without hematuria much like the typical signs and symptoms associated with Wilms' tumor. Abdominal pain and fever may also occur. In some instances, patients present with pathologic fractures due to metastatic tumor.

Pathology
Grossly, the tumor arises within the renal medulla has a mass of up to 3,000 grams. On cut section, the tumor is usually white-tan to gray and has a firm texture and is sharply defined from the surrounding renal parenchyma. Histologically, the classical CCSK (features present at least focally in over 90% of tumors) is composed of nests and cords of cells with scant cytoplasm and high nuclear-cytoplasmic ratios. The tumor has a prominent vascular network that may be highlighted with Ulex European I lectin or monoclonal antibodies specific for factor VIII or CD31. Adundant collagenous (sclerotic) extracellular matrix material is also a common finding in classical CCSK. The nuclei are characterized by a fine chromatin pattern and mitotic figures are generally rarely identified. Isolated nephrons are entrapped by the tumor. CCSK may be confused with Wilms' tumor, mesoblastic nephroma, and malignant rhabdoid tumor of the kidney.
Several histologic variants of CCSK are recognized. The most common variant is the myxoid CCSK. This histology features diffuse accumulation of mucopolysaccharide matrix material between tumor cells sometimes creating a cystic appearance. The sclerosing variant of CCSK is characterized by prominent collagen bundles that may isolate single or small groups of tumor cells in a dense matrix that may become hyalinized. The cellular pattern of CCSK is characterized by less extracellular matrix material between cells with overlapping of nuclei, a feature that may lead to confusion with a blastemal predominant Wilms’ tumor or primitive neuroectodermal tumor. Mitotic activity is usually increased in this variant. The epithelioid CCSK variant may be confused with nephroblastoma due to condensation of tumor cell cords. The palisading pattern is described as having spindle cell nuclei in parallel linear arrays alternating with nuclear free zones, a feature that resembles Verocay bodies of schwannomas. The spindle cell and storiform patterns are relatively uncommon. Anaplasia is a rare finding in CCSK (3% of cases), and is characterized by the presence of enlarged, hyperchromatic polypoid nuclei with multipolar mitotic figures. The nuclear accumulation of p53 in anaplastic tumors is thought to represent evidence of p53 gene mutation, a finding that has been well-documented in anaplastic Wilms’ tumors. The frequency of different CCSK variants is listed below:

- Myxoid pattern (50%);
- Sclerosing pattern (35%);
- Cellular pattern (26%);
- Epithelioid pattern (trabecular or acinar type) (13%);
- Palisading (verocay-body) pattern (11%);
- Spindle cell pattern (7%);
- Storiform pattern (4%);
- Anaplastic pattern (2.6%).

Immunohistochemistry is rarely informative in CCSK. Immunoreactivity for the intermediate filament vimentin is usually present, however, reactivity with most other proteins including epithelial markers are negative.

Like other renal tumors of childhood, CCSK is staged by the National Wilms’ Tumor Study staging scheme as follows:

**Stage I (25% of CCSK):** For stage I tumors, 1 or more of the following criteria must be met:
- The tumor is not ruptured or biopsied (open or needle) prior to removal.
- No involvement of renal sinus vessels.
- No residual tumor apparent beyond the margins of excision.

**Stage II (37% of CCSK):** For Stage II tumors, 1 or more of the following criteria must be met:
- Tumor extends beyond the kidney but is completely excised.
- No residual tumor apparent at or beyond the margins of excision.

Any of the following conditions may also exist:
- Tumor involvement of the blood vessels of the renal sinus and/or outside the renal parenchyma.
- The tumor has been biopsied prior to removal or there is local spillage of tumor during surgery, confined to the flank.

**Stage III (34% of CCSK):** For Stage III tumors, 1 or more of the following criteria must be met:
- Unresectable primary tumor.
- Lymph node metastasis.
- Positive surgical margins.
- Tumor spillage involving peritoneal surfaces either before or during surgery, or transected tumor thrombus.

**Stage IV (4% of CCSK):** defined as the presence of hematogenous metastases (lung, liver, bone, or brain), or lymph node metastases outside the abdominopelvic region.

**Stage V (not yet reported for CCSK):** defined as bilateral renal involvement at time of initial diagnosis.

**Treatment**

Treatment of CCSK generally involves surgical intervention coupled with radiation and chemotherapy. CCSK commonly responds poorly to treatment with vincristine and actinomycin alone, but the addition of doxorubicin to chemotherapy regimens has improved survival rates. In the NWTS-5 protocol, patients with all stages of CCSK are treated with the same regimen used in patients who have Wilms tumor with diffuse anaplasia with the exception of stage I tumors. This treatment protocol is comprised of radical nephrectomy followed by radiotherapy and chemotherapy with cyclophosphamide, etoposide, vincristine, and doxorubicin for 24 weeks.

**Prognosis**

The prognosis for CCSK, particularly for low stage tumors, has improved with the addition of doxorubicin to chemotherapy regimens with a 66% reduction in overall mortality. Stage-dependent six-year survival is 97% for stage I tumors, 75% for stage II tumors, 77% for stage III tumors, and 50% for stage IV tumors.

Patients with tumors without areas of necrosis have a more favorable prognosis. Twenty-nine percent of patients with CCSK have lymph node metastases at the time of diagnosis, and bone metastasis is the most common form of relapse. Metastatic lesions have also been reported in the liver, brain, soft tissue sites, and lung with more unusual metastases to the skeletal muscle, testis, and salivary gland. Relapses of CCSK as many as 10 years after original diagnosis have been reported.
Kidney: t(10;17) in clear cell sarcoma of the kidney

Brownlee NA et al.
Atlas Genet Cytogenet Oncol Haematol. 2006;10(1)

Cytogenetics

Note: Only a small number of CCSK cases have been described cytogenetically. A clonal reciprocal 10;17 translocation t(10;17)(q22;p13) in CCSK was first reported in 1989. A CCSK with a complex karyotype including trisomy 9, deletions of chromosomes 16 and 22, and loss of chromosome 1p13 has been reported. In the same case, an interstitial deletion of chromosome 14 was reported: del(14)(q23). One of two sarcomatous Wilms' tumors also contained a t(10;17)(q11;p12) as a part of an abnormal karyotype. Three of four other patients with CCSK were normal whereas one patient harbored a t(2;22)(q21;q11). Comparative genomic hybridization analysis of CCSK has documented quantitative chromosomal abnormalities in only 4 of 30 CCSK cases. These four cases included a gain of chromosome 1q and loss of 10q, gain of 1q and loss of terminal 4p, gain of 19p, and loss of chromosome 19. Later, another CCSK with a t(10;17)(q22;p13) was reported.

Of five patients reviewed at this institution, karyotypes were available for four of these. One patient had a clonal balanced translocation 10;17 and an interstitial deletion of the long arm of chromosome 14 as follows: 46, XY, t(10;17)(q22;p13)del(14)(q24.1q31.1). Three other patients had normal karyotypes. Fluorescent in-situ hybridization using a p53 probe was employed on the same cells harboring the clonal translocation above. This study documented the presence of two p53 signals on chromosome 17 indicating the absence of deletion or translocation of the TP53 tumor suppressor gene.
Genes involved and Proteins

**Note:** No gene has been implicated in the pathogenesis of CCSK. However, given the recurrent finding of clonal balanced translocations involving t(10;17)(q22;p13), gene(s) located within these regions may be related to CCSK pathogenesis. The chromosome 17p13 locus harbors the TP53 tumor suppressor gene, but several studies have failed to implicate mutations of p53 in CCSK. Tumor suppressor and oncogenes present on chromosome 10q22 include LCX and TET1. Both of these genes are involved in fusion gene products in acute myeloid leukemias. Tumor suppressor and/or oncogenes located in the deleted region of chromosome 14q24.1q31.1 include CHES1, a member of the forkhead family of transcription factors involved in cell cycle checkpoint control, hREC2, a gene encoding a protein with amino acid homology to a RAD51 involved in DNA double strand break repair, MAP3K9 or mitogen activated protein kinase, the MAX transcription factor, placental growth factor (VEGF-related protein), and transforming growth factor beta-3.

References


This article should be referenced as such:

Turcot syndrome
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Identity

Other names: Malignant tumors of the central nervous system associated with familial polyposis of the colon.

Note: Turcot syndrome (TS) is characterized by the association of colonic polyps and central nervous system tumors. The relative risk of cerebral tumor in patients with familial adenomatous polyposis is considered 92 times more than found in the general population. The predominant brain tumors are medulloblastoma and gliomas.

Inheritance: Both autosomal dominant and autosomal recessive modes of inheritance have been described, based on the analysis of familial segregation of the disease and the results of molecular studies. Nevertheless, considering the low penetrance and rarity of TS, the involvement of a major gene in association with a second locus containing a modifier gene or of environmental factors has been suggested.

Clinics

Neoplastic risk

Cardinal findings in TS are colonic polyps with tendency to colorectal cancer and malignant central nervous system tumors.

Colonic polyps: Three types of polyposis coli are described to occur in TS: 1) Type 1 is characterized by multiple colonic polyps numbering between 20 and 100, some of which may exceed 3 cm in diameter; 2) Type 2 is characterized by a small number of colonic polyps, usually less than 10; 3) Type 3 is characterized by numerous small colonic polyps similar to those of classical familial polyposis coli. Based on molecular entities, two groups can differentiated: the one due to mutation in the APC gene (see below), characterized by colorectal adenomas without polyposis. Colorectal cancer: the polyps frequently show malignant transformation in the second and third decades of life.

Central nervous system tumors: Two major types of TS are distinguished based on different types of central nervous system tumors. The first one is characterized by childhood cerebellar medulloblastoma and the second by gliomas, particularly glioblastoma multiforme, arising in both children and adult. The two different types are related to different molecular pathogenesis. In fact, the first type is caused by mutations in the APC gene (see below), whereas the second type is related to MMR genes mutations (see below).

Other: In some instances, patients with TS have additional symptoms characteristic of other genetic conditions with familial polyposis of the coli, including pigmented ocular fundus lesions, epidermal inclusion cysts, osteosclerotic jaw lesions, cafe-au-lait spots or lipomas.

Cytogenetics

Note: Chromosome analysis is generally normal in patients with TS.

Genes involved and Proteins

APC (Adenomatous Polyposis of the Colon)

Location: 5q21

Note: The APC locus consists of 15 exons.

Protein

Function: APC: APC seems to be involved in cell adhesion with a role in the beta-catenin -APC interaction. It is possible that the APC complex...
regulates transmission of the contact inhibition signal into the cells, since APC mutations are associated with the development of hyperplasia, an early event in tumorigenesis. Alternatively, it is possible that the APC-catenin complex regulates adhesions, since loss of cadherin-mediated adhesion can contribute to metastasis.

**Mutations**

Germline APC mutations are detectable in 2/3 of patients with TS. In the remaining patients, germline mutations in MMR genes can be found. Molecular analysis have shown that heterozygous, homozygous or compound heterozygous mutations may be implicated in TS. TS caused by APC mutations is associated with childhood cerebellar medulloblastoma and colonic polyps, while TS related to MMR genes is associated with glioma and colorectal adenomas without polyposis. Nevertheless, there is a wide clinical heterogeneity among carriers of mutations in the same gene, and even among pedigrees segregating for the same molecular defect. Such variations could be accounted for by genetic or environmental modifiers.

**MLH1**

**Location:** 3p21.3

**Note:** The MLH1 locus encompasses approximately 100 kb and consists of 19 exons.

**Protein**

Function: MMR genes: MLH1 and PMS2 are involved in DNA mismatch repair, and neoplasms of affected patients show DNA replication errors.

**PMS2**

**Location:** 7p22

**Note:** The PMS2 locus encompasses 16 kb and consists of 15 exons

**Mutations**

PMS2 mutations have been identified in a few families so far, and a very severe phenotype has been described in most of the cases.

**References**


This article should be referenced as such:

Spatial arrangement of the human genome and its possible functional role

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1. Introduction

In eukaryotic cell nuclei genomic DNA interacts with histones to form nucleosomes; arrays of nucleosomes are packaged into chromatin fibers that constitute chromatin in interphase cell nuclei, chromatides and chromosomes in mitotic cells. In the chromatin of the cell nucleus chromosome territories can be distinguished occupying well defined nuclear subvolumes (for review see Cremer and Cremer, 2001). Chromatin mediates gene expression in response to external or internal signals that induce complex patterns of enzyme-catalyzed chromatin modifications, such as DNA methylation by DNA methylases, histone phosphohorylation by kinases, acetylation/deacetylation of histone tails by histone-acyetyltransferases and deacetylases, methylation by histone-methyltransferases, ubiquitination by Ub-ligases, etc (see e.g. Howe et al., 1999; Berger, 2001; Jenuwein and Allis, 2001). These epigenetic modifications lead to complex changes of the physico-chemical properties of chromatin, including steric effects on the chromatin structure and formation of recognition sites for other proteins. Distinct histone tail modifications can generate synergistic or antagonistic interaction affinities for chromatin-associated proteins, which in turn dictate dynamic transitions between transcriptionally active or transcriptionally silent chromatin states.

The combinatorial nature of histone amino-terminal modifications has led to the concept of a "histone code" that considerably extends the information potential of the genetic code (Strahl and Allis, 2000, Jenuwein and Allis, 2001). These results support the hypothesis that epigenetic chromatin modifications and concomitant changes of the 3D structure of chromatin from the level of chromatin loop domains via chromosomal territories (CTs) to suprachromosomal organization of the genome are responsible for the transition of the transcriptionally silent chromatin into active chromatin states and vice versa (Cremer and Cremer, 2001).

An important role in nuclear architecture and gene silencing plays the condensed chromatin that is called heterochromatin (Heitz, 1928). Constitutive heterochromatin is virtually free of protein coding genes and mostly located in peri- and paracentromeric chromosomal subregions. Facultative heterochromatin contains silent genes. The presence of different chromocentres in cell nuclei (spatial associations of centromeric heterochromatin), "myeloid" (in monocytes and granulocytes) and "lymphoid" (in lymphocytes), was found by Albobia et al. (2000; 2003) suggesting cell type specific and ontogenically determined organization patterns. Recruitment of genes into the close neighborhood of constitutive heterochromatin or packaging into facultative heterochromatic chromatin domains represents an important mechanism of epigenetic regulation of gene silencing (Grewal and Elgin, 2002; Francastel et al., 1999; Bartova et al., 2001). On the other hand, tissue-specific enhancers and locus control regions (LCRs) prevent active genes from being included in a region of transcriptional inactive condensed chromatin (heterochromatin) that forms during cell maturation (Bulger and Groudine, 1999; Francastel et al., 2000).

One pathway of heterochromatin formation is apparently related to histone H3 lysine (K) methyltransferases (HMTases), stably modifying histones H3 by methylating lysine at 9 position (Lachner and Jenuwein 2002). H3-K9 methylation creates a binding site for the (chromo) domain of heterochromatic HP1 proteins. These findings have suggested existence of a biochemical mechanism for induction and propagation of subdomains of facultative heterochromatin (for review see Lachner and Jenuwein 2002). Heterochromatic domains are maintained by...
highly dynamic HP1 binding and, consequently, silent genes are easily accessible to individual regulatory factors (Cheutin et al., 2003; Festenstein and Aragon, 2003). The absence of HP1 in human granulocytes with highly condensed chromatin suggests another pathway of heterochromatin formation (see chapter 6.1).

Our understanding of the mechanisms of formation and the role of chromatin higher-order structures is obviously very poor to allow explanation of the large scale genome architecture and its function. Therefore, a simple description of the genome arrangement and its changes is needed in order to consider relationships and deduce mechanisms. In the subsequent chapters the following topics will be discussed:

(i) the global structure of the human genome,
(ii) the structure and orientation of chromosome territories in cell nuclei,
(iii) the dynamics of the human genome arrangement,
(iv) tethering of chromosome territories and
(v) changes of the genome and territory structure during important cellular processes such as the cell cycle, cell differentiation, apoptosis, cell transformation etc.

2. Orderliness and Randomness in the Global Structure of the Human Genome

Visualization of CTs by fluorescence in situ hybridization (FISH) in mammalian and plant cells (Scharadin et al., 1985; Pinkel et al., 1988; Cremer et al., 1988; Lichter et al., 1988) lead to intensive investigations of the structure of human genome. Studies of the arrangement of the human genome and CTs have been performed for 20 years using 2D or 3D FISH in fixed cells (for reviews see Cremer and Cremer, 2001; Parada and Misteli, 2002). Recently, experiments using incorporation of labeled precursors or GFP tagged proteins binding DNA (e.g. histone H2B-GFP) provided additional information on the structure and dynamics of the human genome (Kanda et al., 1998; Bornfleth et al., 1999; Edelman et al., 2001; Kimura and Cook, 2001; Chubb et al., 2002; Walter et al., 2003; Gerlich et al., 2003). Both 3D FISH and live cell approaches have their specific advantages and limitations and it is important to explore both approaches in parallel. For example, the 3D FISH approach is particularly suited to study the topology of a large set of active and inactive genes with respect to higher order euchromatic and heterochromatic compartments. A potential drawback of 3D FISH is represented by the fact that considerable chromatin damage produced by this procedure can be expected at the level of chromatin fibers. However, the level of preservation of the nuclear topography even after the heat denaturation step is sufficient to study the large scale chromatin topology (Solovei et al., 2002). Similar nuclear topography has been found even after repeated FISH (Falk et al., 2002).

2.1. 3D Structure of the Human Genome in the Cell Nucleus is not Random

Investigations of the nuclear topology of centromeres started very early using indirect immunofluorescent labeling with anticientromere antibodies (Hadlaczky et al., 1986; Weimer et al., 1992) and later using confocal microscopy (e.g. Popp et al., 1990; Hulspas et al., 1994; Höfers et al. 1993; Skalnikova et al., 2000). Paracentromeric chromosome regions were found either randomly distributed in the volume of the cell nucleus or localized near the nuclear periphery. Investigations of the 3D topography of genes in cell nuclei started much later (Kozubek et al., 1997; Lukasova et al., 1997; Parreira et al., 1997). Most genes were found in the nuclear interior in striking contradiction to distributions generated from random models. In addition, tethering of genes was found and suggested as a mechanism for increased induction of chromosome aberrations in specific cases (Kozubek et al., 1997), which was confirmed in several other contributions (Kozubek et al., 1999a; Nikiforova et al., 2000; Parada et al., 2002). Systematic studies that were performed more recently involved determination of nuclear radial positions of all chromosomes (Bartova et al., 2001; Boyle et al., 2001; Boltzer et al., 2005) and also other genetic elements such as arms or other regions of chromosomes, centromeres, telomeres and some genes (Skalnikova et al., 2000; Cremer et al., 2001; 2003; Kozubek et al., 2002; Amrichová et al., 2003).

Investigations of the relationships between nuclear positioning of genetic elements and their other characteristics showed the correlation between gene density or activity of the chromosome region and its radial location in the cell nucleus (Croft and Brooks, 1999; Boyle et al., 2001; Cremer et al., 2001; Tanabe et al., 2002; Kozubek et al., 2002; Cremer et al., 2003). Genes of highly expressed CT regions are localized in the central parts of the cell nucleus; sequences or regions with low expression are found preferentially near the nuclear periphery. In cells with adherent growth another relationship was found - the so called size dependent positioning of chromosome territories (Sun and Yokota, 1999). This finding is currently a subject of discussions (Bolzer et al., 2005). Correlation was found between transcription activity and replication timing (Sadoni et al., 1999). It was shown that distinct higher order compartments whose DNA displays specific replication timing were stably maintained during all interphase stages. Transcriptionally competent and active chromatin was confined to a coherent compartment within the nuclear interior that comprised early replicating R-band sequences. G/C-bands were located mostly on the
nuclear periphery (including perinucleolar compartments). The average centre of the nucleus to genetic element distances were found to be elementspecific, largely maintained in different cell types and even evolutionarily conserved (Habermann et al., 2001; Kozubek et al., 2002; Tanabe et al., 2002; Cremer et al., 2003). It has been shown in yeast that the tethering or targeting of a silencer-flanked reporter gene to the nuclear envelope facilitates its repression (Andrulis et al., 1998). On the other hand, association with the nuclear periphery is not sufficient if the reporter construct has no silencer element (Gasser, 2001).

Radial nuclear distributions, illustrating nuclear topography of high gene density (expression) and low gene density regions of chromosomes, are shown in Fig. 1 as a superposition of a large number of measurements in central nuclear sections. The density of points represents the probability density per volume unit of genetic region occurrence at a given position. The figure demonstrates distinct radial distributions of genetic regions in cell nuclei. Highly expressed chromosome regions are found close to the centre of the cell nucleus; while regions with low expression are localized close to the nuclear membrane (Kozubek et al., 2002; Lukasova et al., 2002; Galiova et al., 2004). It is worth to note that while the density of points is maximal in the center of the cell nucleus (Fig. 1 A), the radial distribution is near to zero in the center of the nucleus (Fig. 1 A1) owing to a very small volume of the central shell.

Thus currently available data support the view that the cell nucleus is far from being a randomly arranged bag of molecules (Croft and Brooks, 1999; Boyle et al., 2001; Cremer et al., 2001; Tanabe et al., 2002; Kozubek et al., 2002; Cremer et al., 2003). On the other hand, the high degree of variability observed among nuclei with stained genetic elements leads to the conclusion that the order in the nuclear organization is manifested rather through statistical regularities. Genetic elements are localized in concentric layers (shells) in cell nuclei which are different for various elements but similar for given element in various cell types (Kozubek et al., 2002). These layers are formed in late telophase/G1 phase and do not depend on gene expression (Ferreira et al., 1997). Decondensation of chromosomes proceeds in radial direction (Manders et al., 2003), which probably forms final structure with specific radial positions of genetic elements; this structure is maintained through the subsequent interphase (e.g. Walter et al., 2003).

Fig. 1. Illustrative radial distributions of the positions of high gene density (A) and low gene density (B) chromosome regions in the cell nucleus. The central section of the cell nucleus is shown with x-y positions of the regions overlaid from a large number of measurements in nuclei with similar radii. The density of points represents the spatial probability density of the occurrence of the region in the particular point. The histograms in the inserts represent radial distributions, i.e. the distribution of probabilities to find the region at particular distance from the center of the nucleus. The vertical bars correspond to the number of points in the shells shown in the cell nuclei. The radial distributions are non-random and different for various genetic regions.
2.2. The Randomness in CTs Neighbourhood and Radial Symmetry of the Cell Nucleus

Mutual positioning of CTs in the cell nucleus is highly variable (Cremer and Cremer, 2001). This fact is evident for everybody from the first observation of mutual positions of two pairs of CTs (or other loci) painted by different fluorochromes. More exact investigation of this variability can be based on the determination of fluorescence weight centers of CTs in 3D space and calculation of the angle CT1-centre-CT2 in the plane defined by these 3 points. Random mutual positioning of CTs is reflected in the angular distribution corresponding to the sine function (Kozubek et al., 2002). In 3D space, the most frequent angle is 90° owing to the fact that the number of possible CT positions corresponding to this angle is the largest (Fig. 2). Obviously the number of free positions for CTs will be proportional to the length of the circle perpendicular to the plane of the image corresponding to angle, that is 2 sin(α). Angular distributions reminding of the sine function (Fig. 2, insert) have been found for a number of different homologous and heterologous pairs of genetic elements (Kozubek et al., 2002; Amrichova et al., 2003), which suggests that in most cases CT mutual positions are random. This type of randomness in the location of CTs is largely responsible for the variability of cell nuclei.

It is important to note, that the existence of the radial arrangement of the cell nucleus which is mentioned in a number of articles (Tanabe et al., 2002; Cremer et al., 2003; Kreth et al., 2004) does not follow from the specificity of radial distributions (the eyes in the human face can be also characterized by some specific radial distribution but we do not say that the face has radial arrangement). In order to say that an object has radial symmetry, some periodicity in angular direction has to be observed. In the case of cell nucleus this periodicity follows from the randomness of angular distributions.

Angular randomness of chromosome positions (positions of other genetic elements) arises probably during the formation of cell nuclei in late telophase/G1 phase of the cell cycle (Walter et al., 2003). Interphase chromatin is relatively stable with restricted movements that might, however, also contribute to finally random angular chromosome positioning during several cell generations.

3. Structure and Orientation of CTs in the Cell Nucleus

The arrangement of interphase chromosomes into separate territories provides a framework for investigations of the relationship between the interphase chromosome structure and function. The basic question is whether gene expression is determined, at least in part, by the structure of the chromosome territory. The studies trying to resolve this issue are aimed at determining whether the organization of CTs is random, whether particular genomic sequences occupy special positions within chromosome territories, whether these positions differ according to the transcripational activity of the sequences and whether genomic regions or whole individual chromosomes occupy particular compartments within the cell nucleus (Sachs et al., 1995; Belmont and Bruce, 1994, Nagle et al., 1995, Ferreira et al., 1997; Lamond and Ernshaw, 1998; Belmont et al., 1999; Cockel and Gasser, 1999; Croft and Brooks, 1999; Sadoni et al., 1999; Verschure et al., 1999; Nagle et al., 2000; Volpi et al., 2000; Chevret et al., 2000; Cremer et al., 2000; Cremer and Cremer, 2001; Sadoni et al., 2001; Tumbar and Belmont 2001; Chubb et al., 2002; Walter et al., 2003; Gerlich et al., 2003).

3.1. Random-walk models

The first systematic quantitative studies of the topology of genetic elements in cell nuclei (Engh et al., 1992; Trask et al., 1993; Yokota et al., 1995; Sachs et al., 1995) lead to the conclusion that CTs could be represented by randomly walking polymers. The authors measured average spatial distances between two genetic elements (Ds) with known molecular distance (m) and showed linear dependence Ds2(m), with the simplest explanation - a random flight
polymer. In a later model of the interphase chromosome two levels of randomness were distinguished: Randomly walking loops of DNA (level 1) attached to a flexible and randomly walking backbone (level 2). This model explained behaviour of the two components of the dependence $D_{2}(m)$. Experiments were performed very carefully with high statistics using methanol 2D fixation as well as 3D paraformaldehyde fixation. In spite of the fact that the analyzed chromosome 4 and 15 territories are relatively gene poor and not highly expressed, these studies represent a basis for further thought.

3.2. CTs are Polar and Oriented in Cell Nuclei

Investigation of the higher-order compartmentalization of chromatin according to its replication timing suggested a polar orientation of early and late replicating sub-regions of chromosomes (Ferreira et al., 1997; Sadoni et al., 1999), with transcription competent and active chromatin located within the nuclear interior. Recent results have demonstrated existence of an important factor influencing nuclear location of a genetic element, which is concentration of highly expressed genes in the molecular environment of an element on the chromosome (Lukasova et al., 2002). Density of highly expressed genes in the environment can be established according to Caron et al. (2001). If a genetic element is located in a region rich in highly expressed genes, its nuclear location is close to the nuclear centre. If it is located in a region poorly populated with expressed genes, its nuclear position is more peripheral.

Regions of high expression that protrude from the more condensed parts of the chromosome located in the proximity of the nuclear membrane to the nuclear centre determine the polar character of CTs which can be directly shown by measurements of 3D positions of at least 3 genetic elements along the territory, e.g. a centromere and both telomeres. Polar nature of CTs has been directly shown for HSA 3, 8, 9, and 19 (Amrichova et al., 2003), where centromeres were localized on one side of the territory and both telomeres on the other side (Fig. 3). Chromosomes are polar independently of their positions inside cell nuclei, i.e., regardless of whether they are located near the membrane or in the centre of the cell nucleus. In addition, a majority of the polar chromosome territories are oriented in the cell nucleus with the centromere localized near the nuclear periphery and both telomeres placed in the interior of the cell nucleus. Only 5-10% of chromosome 8 and 9 territories showed the opposite orientation.

Chromosome polarity and orientation can also be deduced from experiments with induced transcription performed in fixed cells (Volpi et al., 2000) or in living cells (Tumbar and Belmont, 2001). Targeting the VP16 acidic activation domain (AAD) to an engineered chromosome site resulted in its transcriptional activation and redistribution from a predominantly peripheral to a more interior nuclear localization. Direct visualization in vivo revealed that the chromosome site normally moves into the nuclear interior transiently in the early G1 and again in the early S phase. In contrast, VP16 AAD targeting induced this sites permanent interior localization in the early G1. These results show that at least active CTs must be polar and oriented in cell nuclei.

Fig. 3. 3D structure of the interphase chromosome. As a typical example, the structure of chromosome 8 in the nucleus of G0 - lymphocytes is shown. The positions of centromeres (grey circles), p-telomeres (red circles) and q-telomeres (green circles) were determined for 275 nuclei in 3D space and placed to the x-y plane in such a way that all chromosomes are superimposed to each other (with minimal deviations of the distances inside clusters of points). Pink, cyan, blue and yellow circles represent the weight centres of all measured p-telomeres, q-telomeres, centromeres and chromosome territories respectively. The figure shows directly the polarity of the chromosome territories (both telomeres are located near to each other on one pole of the chromosome territory, the centromere being on the opposite pole).
4. Dynamics of the Human Genome Structure, the Cell Cycle

Stability of interphase chromatin has been suggested from early experiments already in the beginning of the 20th century (Boveri, 1909). This observation was recently confirmed by different methods in several contribution (Shelby et al., 1996; Zink and Cremer, 1998). For example, mirror images of daughter cells obtained after FISH have also lead to the conclusion that the mobility of chromatin in interphase cells is rather restricted (Kozubek et al., 1999b; Sun and Yokota, 1999). Experiments with living cells showed a high degree of stability of the interphase chromatin arrangement from G1 to G2 stages of the cell cycle and, to some extent, transmission of chromosome positions from mother to daughter cells (Gerlich et al., 2003; Walter et al., 2003). The authors admit that some intermixing that occurs within one cell division may lead to randomizing of CTs positions over several cell cycles. Constrained chromatin motion due to the likely association with nuclear compartments in human cells was shown using lacO integrant cell lines (Chubb et al., 2002). The loci at nucleoli or the nuclear periphery were significantly less mobile than other, more nucleoplasmic loci. Conserved positioning of HP1-GFP foci during interphase (Ondrej et al., submitted) is illustrated in Fig. 4; time-lapse measurements demonstrated diffusion coefficients of $1 \times 10^{-6} \text{m}^2/\text{s}$ (similar to slowly moving loci of Chubb et al., 2002) restricted to the range of 0.1 m; directional movements were observed for longer time intervals.

Although CTs in the cell nucleus are relatively immobile, certain restricted movements or imprecise transitions through mitosis have been observed (Zink et al., 1998; Chubb et al., 2002; Walter et al., 2003; Gerlich et al., 2003). Movements inside CTs have also been observed in living cells (Tumbar and Belmont 2001) due to transcriptional activation. These results show that stable global interphase arrangement found by other groups (Walter et al., 2003; Gerlich et al., 2003) may be perturbed by central movement of relatively small chromosome regions. Consequently, the question arises how firmly are genetic elements attached to CTs (or the nucleus) during these movements and what is the proportion of movements of CTs as a whole and movements of genetic elements inside the territories.

Visualization of several genetic elements inside CTs has shown that their positioning can be either dependent or independent on the positioning of CTs (Amrichova et al., 2003). After rotation of the cell nucleus and transition of the weight centres of the investigated painted territories to a single point territorial distribution of genetic elements can be seen. The width of these distributions is usually narrower as compared with radial nuclear distributions. This means that the elements adhere to the territory. For example territorial distribution of q-telomeres of HSA 19 in Go-lymphocytes is narrower in comparison with nuclear distribution, which means that the q-telomere is quite firmly attached to the chromosome territory (Fig. 5).

![Fig. 4. The localization and movement of HP1 foci in the space of the cell nucleus. (A) XY, XZ, and YZ projections of the nucleus of MCF7 cell transfected with HP1-GFP and H2B-HcRFP is shown. (B) Positions of the HP1 foci were found by the computer at different time points (with 40 min intervals). The positions were corrected for movement and rotation of the nuclei using H2B-RFP. As a consequence of the restriction of movement of HP1 foci, the positions at different time intervals form easily distinguishable clusters.](image-url)
The opposite possibility is a broader territorial distribution, which means that the corresponding genetic element, not adhering to the territory; may be attached to other nuclear structures. This extreme possibility is represented by the behaviour of the p-telomere of HSA 19 in stimulated lymphocytes which shows full independence in relation to its own chromosomal territory. These findings show that elements may be attached either to the territory or to the nucleus. This may be explained by the fact that telomeres and telomere-specific binding proteins may associate with the nuclear matrix and participate in anchoring chromosomes. In addition, the decondensation of chromatin related to high concentrations of expressed genes may cause extension of the distances between genetic elements in the cell nucleus and contribute to the relative independence of an element in relation to its territory.

In prometaphase, chromosome rosettes are formed by centromeres joining together and forming a central ring. Nagele et al. (1995) found a precise arrangement of CTs along the ring with homologous CTs being localized on the opposite sides of the ring. These results were not confirmed by Allison and Nestor (1999) who found random positioning of CTs in metaphase rosettes. In our experiments using nocodazole to block HL-60 cells in prometaphase we were not able to reproduce the precise chromosome order described by Nagele et al., (1995), even though the positions of centromeres were not random, rather showing a trend towards a preferential order.

5. Tethering of Chromosome Territories

In some cases, non-random angular distribution of homologous and heterologous elements was found (Kozubek et al., 2002). Shorter distances than predicted by random distribution were found between BCR/BCR genes located on homologous acrocentric chromosomes or between BCR/PML belonging to heterologous acrocentric chromosomes. Acrocentric chromosomes participate in the formation of the nucleolus and this common function may influence their nuclear location and lead in some cases to mutual proximity.
Tethering of CTs is well known for centromeres that are frequently localized in chromocentres whose number per cell nucleus is in some cases substantially smaller than 46 (Alcobia et al., 2000). Centromeres are most frequently localized near the nuclear periphery or near the nucleoli. Nucleoli are thought to represent another example of inner nuclear surface where chromosomes can be attached (Sadoni et al., 1999). Association of centromeres is thought to play an important role in formation of heterochromatic foci and in gene silencing (see the section on heterochromatin). Physiological telomere associations were found frequent in interphase nuclei of human fibroblasts (Nagele et al., 2001) and less frequently in cycling cells. This was a reason to assume that telomeric associations may be involved in the maintenance of chromosome positional stability in the interphase nucleus, especially in cells that are proliferating slowly, replicatively quiescent, or terminally differentiated. The authors thus conclude that the number of telomere associations in interphase nuclei depends on the cycling status of the cell, rather than on the individual telomeres length and telomerase activity. Using specific DNA probes, telomere association of CTs 8, 9, and 19 was investigated in Amrichova et al. (2003). No association between heterologous telomeres was found. On the other hand, homologous telomeres of CT 19 were often close to each other and signals of both telomeres (p-p or q-q) could often be identified as a single spot. This phenomenon was highly prevalent but did not depend on the stage of the cell in the cell cycle. Owing to telomere association, their central localization (Amrichova et al., 2003) and high level of gene expression in their neighborhood (Quina and Parreira, 2005), the associations of telomeres observed in the interphase nucleus might contribute, as opposed to chromocenters, for the establishment of transcription-permissive 3D nuclear compartments. Experimental distributions of minimum distances between ABL-BCR in human lymphocytes differ from theoretical predictions (Kozubek et al., 1999a; 2002); distribution of these distances is shifted to lower values. In about 10-25% of Go-lymphocytes of 5 healthy individuals the minimum distance between ABL and BCR genes was less than 1 m. No translocation between these genes was found in metaphases of stimulated lymphocytes from these individuals. The shift of distance distributions for the ABL and BCR genes was not observed for stimulated lymphocytes and HL-60 cells, even though tethering was observed for CD34+ progenitor cells. Proximity of specific chromosome regions can lead to their mutual rearrangement under some conditions, as shown for RET/H4 (Nikiforova et al., 2000). Our results obtained in 2D (Kozubek et al., 1999a) or 3D (Kozubek et al., 2002) show very close proximity of ABL/BCR genes (< 1 m) in about 15-20% of Go-lymphocytes. Proximity of these regions might be one of the reasons for their interchanges and the formation of the Philadelphia chromosome typical of chronic myeloid leukaemia (Rabbitts, 1994).

The high frequency of interchanges induced by fast neutrons between chromosomes involved in translocations leading to most frequent haematologic malignancies also indicates the non-random arrangement of some chromosomes in cell nuclei (Lukasova et al., 1999; Cafourkova et al., 2001; Bickmore and Teague, 2002).

### 6. Changes of the Genome and Territory Structure During Important Cellular Processes

#### 6.1. Cell Differentiation
Several mechanisms were considered as an explanation of structural modification of gene activity. For example Ikaros, a DNA-binding protein localized in the discrete foci of nuclei of murine B-lymphocytes, is in close association with centromeric heterochromatin. A strong correlation was found between these foci and the location of transcriptionally inactive genes (Brown et al., 1997; 1999). In addition, in the context of differentiation of human lymphocytes a discovery was made that the promoter-specific binding factor of Ikaros mediates association of cell-type-specific genes with centromeric heterochromatin. Ikaros regulates movement of the genes towards centromeric heterochromatin, whereas activated genes are released (Cockell and Gasser, 1999). Thus, gene positioning on the periphery of the chromosome territory could facilitate not only access to the transcriptional machinery (enabling gene activation), but also access to the factors inhibiting genetic expression (e.g., clusters of centromeric heterochromatin).

Spatial dynamics of selected genetic elements was studied during human blood cell differentiation with parallel monitoring of their expression dynamics (Bartova et al., 2000; Bartova et al., 2002; Galiova et al., 2004). The role of the chromatin structure in regulation of the studied gene expression was tested. The following three hypotheses were verified:

1. Activated (silenced) genes change their location in the cell nucleus,
2. Activity of genes correlates with their location within the corresponding chromosome territory, and
3. Gene expression is regulated by the association of genes with centromeric heterochromatin.

It was found that in the process of cell differentiation genetic elements are shifted to the periphery of the cell nucleus (Bartova et al., 2000; 2002; Galiova et al., 2004). However, these changes of the nuclear organization did not correlate with alterations in genetic expression Bártová et al., 2002).
Fig. 6. Distributions of distances between genes and the nearest cluster of centromeres. Simultaneous visualisation of genes and all centromeric regions forming the chromocentres was used to determine distributions for the ABL (A) c-MYC (B) and RB1 (C) genes in undifferentiated cells (HL-60), as well as in terminally differentiated granulocytes (GR). Mean values of the distributions (RGmin) normalised to the nuclear radius and their standard errors are given in each panel. (D) An illustrative example of the nucleus of the HL-60 cell with centromeric heterochromatin (green) and the RB1 genes (red) found in close neighbourhood to one of centromeres. The RB1 gene is not expressed in HL-60 cells.
Independently of gene expression, genetic elements were located closer to the corresponding fluorescence intensity centre of chromosome territory after differentiation, which rather reflects condensation of the CTs (similar shift to the centre of CTs is also observed for centromeres). Genes were located on the periphery of CTs, unlike centromeres, found closer to the bary centre of CTs, which is in agreement with observations of Kurz et al. (1996), who found either active or inactive genes preferentially located on the periphery of CTs. The distributions of distances between the genes and the nearest centromeric heterochromatin revealed a correlation with gene activity (Fig.6). A correlation between transcriptional activities of some tissue-specific genes and their association with pericentromeric heterochromatic regions has been found in several other studies in mammalian cells (Francastel et al., 1999; Fisher and Merkenschlager, 2002). Topography of different genetic loci in human peripheral blood granulocytes was investigated in Bartova et al. (2001). Nuclei of granulocytes are characterized by a segmented shape consisting of two to five lobes that are in many cases connected by a thin filament containing DNA. Granulocytes (neutrophils, basophils and eosinophils) represent an example of terminally differentiated cells with the highest possible condensation of chromatin (Alberts et al. 1994; Grigoryev and Woodcock, 1998). Different topographic types of granulocytes were distinguished on the basis of the pattern of CTs or genetic element segregation into individual lobes. Painting of the same type of chromosome in two-lobed nuclei showed a prevalence of symmetric topographic types (the homolog segregated in one lobe each). The results of the analysis of five topographic types (defined by two CTs pairs in two-lobed nuclei) have shown that symmetric topographic types for both chromosomes are significantly more frequent than predicted by simple statistics. Repeated hybridization experiments have confirmed that the occurrence of certain patterns of chromosome segregation is much higher than that predicted from the combination of probabilities. Both genes and centromeres were observed on filaments joining different lobes. The significance of individual topographic types, particularly of those observed with much higher probability than expected, is unclear.

Fig. 7. Distribution of HP1 in human peripheral blood cells (lymphocytes, monocytes, eosinophiles and neutrophiles) and in human blood progenitor CD34+ cells. HP1 was found in CD34+ cells, lymphocytes and monocytes, but not in neutrophiles and some eosinophiles. The images represent the central XY cuts through the nuclei. Immunodetection was performed using FITC labeled secondary antibodies. DNA was counterstained with TOPRO-3. Inserted histograms represent the level of antibodies signals measured as the mean value of green channel intensity.
Cell differentiation represents also an interesting model for studies of alterations of the genome structure in relation to the formation of heterochromatin and histone modifications (Lukasova et al., 2005). It was shown that common heterochromatin antigenic protein markers such as HP1 and mono-, di-, and trimethylated histone H3 lysine 9 (H3K9), although present in human blood progenitor CD34+ cells, differentiated lymphocytes, and monocytes, are absent in neutrophil granulocytes and to large extent, in eosinophils (Fig. 7). Monomethylated and in particular, dimethylated H3K9 were present to variable degrees in the granulocytes of chronic myeloid leukemia (CML) patients, without being accompanied by HP1 proteins. In patients with an acute phase of CML and in acute myeloid leukemia patients, strong methylation of H3K9 and all isoforms of HP1 are detected. In chronic forms of CML, no strong correlations among the level of histone methylation, disease progression, and modality of treatment were observed. Histone methylation was found even in “cured” patients without BCR/ABL translocation, suggesting an incomplete process of HP1 are detected. In chronic forms of CML, no strong correlations among the level of histone methylation, disease progression, and modality of treatment were observed. Histone methylation was found even in “cured” patients without BCR/ABL translocation, suggesting an incomplete process of developmentally regulated chromatin remodeling in the granulocytes of these patients. The absence of HP1 in human granulocytes that are characterized by highly condensed chromatin strongly suggests another mechanism of heterochromatin formation alternative to that mediated by HP1 binding to H3K9 methylated histones. Thus, at least 2 types of heterochromatin does exist, one being organized by HP1 with fast dynamics (Cheutin et al., 2003) and the other that is more compact and that is could be typical of terminally differentiated non-dividing cells.

6.2. Ionizing radiation (repair of radiation damage), apoptosis

Rearrangement of human cell homologous CTs in response to ionizing radiation was observed by Dolling et al., 1997. In this study, homologous CTs were found closer to each other after irradiation, and the authors proposed that the process of CTs pairing to facilitate recombinational repair of DNA DSBs may exist. In addition, radial movement of genetic elements was observed after irradiation of several cell lines (Jirsova et al., 2001). The spatial relationships between genetic elements returned to that of the non-irradiated controls during several hours of incubation after irradiation. The authors speculated that the changes of the large-scale chromatin structure might be related to repair processes, however, they exclude repair of DSBs by processes involving homologous recombination, because the angular distributions of homologous sequences remained random after irradiation. Radial movement was also observed by Tumbal and Belmont (2001) in live cell experiments.

Nuclear architecture of selected CTs was investigated in apoptotic nuclei of human leukaemia-affected cells (Bartova et al., 2003). Apoptotic disorganization of chromosome territories was irregular, leading mainly to chromosomal segments of different sizes and, consequently, chromosomal disassembly was not observed at specific sites. In comparison to the control group an increased number of centromeric FISH signals were observed in prolonged confluence-treated K-562 cells induced to apoptosis. Sequential staining of the same apoptotic nuclei by the FISH and TUNEL techniques has revealed that chromosome territory segmentation precedes the formation of nuclear apoptotic bodies.

6.3. Haemoblastoses and Cancer

Radial and angular distributions have been measured in both normal and tumour cell lines with similar results. Distributions of ABL and BCR are very similar in bone marrow cells, in Go and stimulated lymphocytes, HL-60 cells, HT-29 colon cancer cells and also in nuclei of colon tissue and CML patients (Koutna et al., 2000). Radial distributions of EWSR1 and FLI1 genes are similar for Go and stimulated lymphocytes as well as for Ewing sarcoma cells (Taslerova et al., 2003). In mouse lymphoma cells two translocated CTs were preferentially positioned in close proximity to each other (Parada et al., 2002). The relative positions of the chromosomes involved in these translocations are close even in normal splenocytes. These observations demonstrate the fact that relative arrangement of CTs in the interphase nucleus can be conserved between normal and cancer cells (see also Cremer et al., 2003). Specific translocations that are (casually) related to some types of leukaemia provide chimeric chromosomes and their nuclear location can be investigated. For example, in Ewing sarcoma cells, radial positions were measured for EWSR1, FLI1 and fusion genes (Taslerova et al., 2003). The radial positions of both fusion genes are shifted compared with the radial positions of non-aberrant EWSR1 and FLI1 genes. While HSA 11 fusion gene is shifted more centrally, HSA 22 fusion gene lies towards the periphery. Thus, both fusion genes are located approximately midway between EWSR1 and FLI1 genes in Ewing sarcoma cells (Fig. 8). The different location of the fusion genes might be explained by the substitution of a small part of HSA 11 for a larger part of HSA 22 and vice versa. The central nuclear location of HSA 22 correlates with its high gene density. Thus, the transfer of a part of HSA 22 with high gene density to HSA 11 causes relocation in the central direction of the translocation neighborhood of chimeric HSA 11. On the other hand, the translocation neighborhood of chimeric HSA 22 is shifted towards the nuclear periphery. In CML, the position of the chimeric chromosome is similar to that of both ABL and BCR loci (Fig. 8).
For the purpose of finding the influence of increased gene expression and amplification in colorectal carcinoma on the chromatin structure nuclear distances between two BAC clones with short genomic separation (1-2 Mb) were measured (using the method called spectral microscopy) and compared between tumor and parallel epithelial cells of 6 patients (Lukášová et al., 2004). Larger nuclear distances were found for tumor as compared with epithelial cells for the same genomic separation. The ratio of the mean nuclear distance between the loci in tumor and epithelium decreased with the mean degree of amplification of genetic loci. Similarly, distances between two exons of dystrophin gene were substantially longer for active X-chromosome as compared to inactive one (Falk et al., 2002). Substantial changes in distances between neighboring loci after locus activation were observed for Hoxb complex (Chambeyron and Bickmore, 2003; Chambeyron et al., 2004).

7. Conclusions
There are several principles of the genome organization in interphase nuclei of human cells that involve a combination of random and nonrandom processes: Genetic elements are localized in concentric layers (shells) in cell nuclei which are different for various elements but similar for given element in various cell types. This arrangement arises during chromosome decondensation in late telophase/G1 phase and forms a general framework for gene expression with more decondensed and consequently centrally located regions with high gene expression. The angular positioning of chromosomes (and consequently of all other genetic elements) is random and consequently the neighborhood of territories may consist of any combination of other territories. This is the reason for radial arrangement of the human genome. In relatively rare cases, chromosome territories can be tethered (e.g. acrocentric chromosomes in nucleoli), which may contribute to higher incidence of specific chromosome exchanges. Chromosome territories consist of chromatin that is relatively stable during interphase with restricted diffusive movement of individual genetic elements. The most stable structure represents heterochromatin that provides silencing of genes. Binding of HP1 protein to methylated H3 histone contributes to the formation of heterochromatin (Cheutin et al., 2003). The HP1 protein is absent in human granulocytes (Lukasova et al., 2005), which strongly suggests that some other mechanism (protein) participates in heterochromatin formation and gene silencing. Randomness in the arrangement of the subregions of a chromosome territory corresponds to the random-walk polymer, however, on the global scale the arrangement of the chromosome territories is nonrandom. Chromosome territories are polar and oriented in the
cell nuclei with more condensed and mostly silent subdomain on the periphery and less condensed and active subdomain in the central parts of the cell nucleus.

The arrangement of the human genome undergoes changes during the cell cycle, cell differentiation, apoptosis, cell transformation and other cellular processes. Condensation of chromatin in mitosis obviously leads to less random but in the same time less functional structure. Cell differentiation and transformation are accompanied by relatively subtle changes in the large-scale genome structure with preserved the main features described above. These changes are, however, of a great importance for gene expression and cell function.

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Spatial arrangement of the human genome and its possible functional role

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This article should be referenced as such:
A new case of t(16;21)(q24;q22) in a secondary AML-M2 following breast cancer therapy

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Clinics

Age and sex: 61 years old female patient.
Previous history: no preleukemia; no inborn condition of note; Breast cancer diagnosed in 2002, treated with radical mastectomy, chemotherapy with cyclophosphamide, epirubicin, 5-fluoro-uracil, radiotherapy.
Organomegaly: no hepatomegaly; no splenomegaly; no enlarged lymph nodes; no central nervous system involvement.

Blood

WBC: 2.4 x 10^9/l; Hb: 10.7 g/dl; platelets: 48 x 10^9/l; blasts: 2%
Bone marrow: Neutrophils 0.05%; Band cells 0.05%; Metamyelocytes 0.13%; Myelocytes 0.02%; Promyelocytes 0.02%; Blasts 0.51%; Late normoblasts 0.13%; Plasma cells 0.01%; Lymphocytes 0.05%; Monocytes 0.01%; Eosinophils 0.02%.

Cytopathology classification

Cytology: AML-M2.
Immunophenotype: Positive for HLA-DR, CD34, CD117, CD13, CD33, MPO, CD56 and CD19; Partial Tdt; Negative for CD7.
Precise diagnosis: Hypoplastic AML, therapy related.

Survival

Date of diagnosis: 04-2005.
Treatment: Three cycles of AraC and Danuribicin; related bone marrow transplantation planned for September 2005.
Complete remission: Yes, 05-2005
Status: Alive (07-2005)
Survival: 3 months

Karyotype

Sample: Bone marrow; Culture time: 24h; Banding: GTG;
Results: 47,XX,+8,t(16;21)(q24;q22)[13]/46,XX[3]

Partial karyotype showing the t(16;21) and a +8

Comments

The t(16;21)(q24;q22) is mainly found in t- MDS /t- AML (14/16 cases (1-10)), following breast cancer therapy (five cases (7,8,10)), lymphoma (four cases), Hodgkin's disease, lung and oviductal cancers and AML-M3 (one case each). Trisomy 8, the secondary change found in the current case, is also reported in most if not all patients with previous breast cancer (7,8,10).
To note, three out of five patients had lymphoid positive antigens (5,7, current case).
All of the nine patients whose treatments were reported (3-9), plus the current case, were treated with a combination of alkylating agents and topoisomerase II inhibitors, +/- radiotherapy.
A new case of t(16;21)(q24;q22) in a secondary AML-M2 following breast cancer therapy

Bruyere H et al.

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This article should be referenced as such: Bruyere H, Yeung W, Tsang P. A new case of t(16;21)(q24;q22) in a secondary AML-M2 following breast cancer therapy. Atlas Genet Cytogenet Oncol Haematol 2006;10(1):56-57.
t(4;12)(q11;p13) in an acute myeloid leukemia without maturation with myelodysplasia

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Clinics
Age and sex: 67 years old male patient.
Previous History: no preleukemia; no previous malignant disease; no inborn condition of note.
Organomegaly: no hepatomegaly; no splenomegaly; no enlarged lymph nodes; no central nervous system involvement.

Blood
WBC: 3.6 x 10^9/l; Hb: 8.6 g/dl; platelets: 151x 10^9/l; blasts: 56%.
Bone marrow: Cellularity fewer than usual. Rare megakaryocytes, presence of micromegakaryocytes. Infiltration by blasts at a level of 58% with myeloid features. Dysgranulopoiesis >10% of non erythoblastic cells.

Cytopathology classification
Immunophenotype: CD34 (85%), HLA DR (91%) and myeloid cluster: CD11c (7%), CD13 (97%), CD13c (99%), CD33 (98%), CD117 (81%), MPO 5% and only one lymphoid cluster CD7 (87%). Conclusion: immature myeloid population. Phenotype FAB M0.
Rearranged Ig or Tcr: Not done.
Pathology: Secondary Acute Respiratory desease due to a bilateral alveolar pneumopathy on June 2005, without suitable microbiological data, following an aplasia phase with fever at D+16 (chemotherapy induction step).
Electron microscopy: No.
Precise diagnosis: AML type Mo with myelodysplasia.

Survival
Date of diagnosis: 04-2005.
Treatment: LAM SA 2002 Protocol. Idarubicine: 15mg per day from J1 to J5 / Aracrytine: 180 mg per day from J1 to J7 / Belustine: 360 mg only at J1 then Aracrytine and Idarubicine each three month during 15 days (6 cures).
Complete remission: Yes during induction phase.
Treatment related death: No.
Relapse: No.
Survival: 5 months.

Karyotype
Sample: Bone marrow; Culture time: 24/48h; Banding: R.
Results: 46, XY, t(4;12)(q11;p13.1) [27]/ 46, XY [3]
Karyotype at relapse: No relapse.

Comments
No AML/ETO t(8;21)(q22;q22) translocation, no split of MLL performed by FISH analysis.
References


This article should be referenced as such:
Educational Item Section

Clinical findings in chromosome aberrations

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I. Prevalence of unbalanced chromosome aberrations Pre-FISH and prometaphase studies

- Newborns 0.3%
- Stillborns 5.0%
- 8th week of gestation 4.2%
- 12th " 2.4%
- 16th " 1.1%
- 20th " 0.8%

II. Chromosome aberrations in spontaneous abortions

- Pre-FISH and prometaphase studies
  - First trimester, total: about 50%, predominantly autosomal trisomies
  - 3 most frequent: triploidy, 45,X, and trisomy 16
- Prenatal ultrasonic findings in autosomal chromosome aberrations
  - Intrauterine growth retardation:
    - Correlates with survival, postnatal growth and mental retardation
May lead to errors in estimation of duration of pregnancy
- Double neck contour
- Abnormal amount of amniotic fluid
- Small placenta
- Congenital malformations
  - Omphalocele
  - Congenital heart defects
  - Renal malformations, large bladder due to urethral obstruction, abnormal male genitalia
  - Cleft lip and palate
  - Holoprosencephaly and other brain malformations
  - Hexadactyly, radial hypoplasia

Reflect disharmonic and/or defective early development of various anatomic structures and allow to determine their onset during prenatal development.
- Often give a hint towards early developmental pathology.
- Masking through major malformations possible.

Localisation: All over the body, especially highly differentiated structures, e.g. facies, male genitalia, distal limbs.
Development:
- Often most impressive in early childhood.
- Tendency to catch-up growth of facial structures.
- In some aberrations marked changes with age.

III. Clinical findings in chromosome aberrations

- Patients with chromosome aberrations always have a distinct clinical picture. They resemble each other as a group.
- Many, but not all chromosome aberrations, cause a highly distinct pattern of abnormalities; patients with these aberrations resemble each other more than their sibs and parents.
- Although there is no “cure” for the adverse impact of chromosomal imbalances on the phenotype (including development), early diagnosis is very important for proper management, prognosis and avoidance of recurrence of chromosome aberrations.
- Chromosome aberrations are characterised by four major criteria:
  - Intrauterine and postnatal growth retardation.
  - A pattern of dysmorphic signs, especially of facies, genitalia and distal limbs.
  - Malformations, often multiple.
  - Impaired mental development/mental deficiency.

IV. Pattern of dysmorphic signs

General:
- Minor anomalies.
- No functional importance, rather of aesthetic importance.
- May be found in healthy and normal individuals as well.
- Characteristic for a given chromosome aberration is a pattern and not a single dysmorphism.

- Reflect disharmonic and/or defective early development of various anatomic structures and allow to determine their onset during prenatal development.
- Often give a hint towards early developmental pathology.
- Masking through major malformations possible.

Localisation: All over the body, especially highly differentiated structures, e.g. facies, male genitalia, distal limbs.
Development:
- Often most impressive in early childhood.
- Tendency to catch-up growth of facial structures.
- In some aberrations marked changes with age.

V. Disappearance of dysmorphisms

- Catch-up growth of nose (Down syndrome, ..).
- Loss of moon facies (5p-,...).
- Catch-up of growth of mandible.
- Loss of epicanthic folds.
- Normalization (horizontalization) of eye position (Down syndrome).
- Loss of deep palmar furrows (trisomy 8).

VI. Onset of dysmorphisms

- Narrow forehead.
- Large, plicated tongue.
- Dysproportionate shortness of metacarpals/metatarsals (Turner syndrome, 5p-).
- Facial asymmetry (5p-).
- Prominent mandible (5p-).

VII. Congenital malformations common to autosomal chromosome aberrations

- Are more variable than dysmorphisms.
- More characteristic than single malformations is a specific combination.
- Discordance rate in monozygotic twins and sibs is high.
- In general, frequent malformations are also frequently observed in chromosome aberrations and vice versa.
- In spontaneous abortions, rare early determined malformations are common.
- Malformations confined to one or very few chromosome aberrations are suspicious for single gene deletions and are therefore interesting for gene zapping.
- Malformations frequent in chromosome aberrations are caused by deficiency of a step in organ development/organogenesis (not: secondary disruption or “false” development).
Clinical findings in chromosome aberrations

Albert Schinzel

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- CNS:
  - Holoprosencephaly
  - Agenesis of corpus callosum
  - Dandy-Walker malformation
  - Spina bifida, lumbar MMC

- Face:
  - Cleft lip, cleft palate
  - Microphthalmia, coloboma
  - Preauricular malformations, reduction of auricles, atresia of auditory canals

- Thoracic:
  - Heart malformations
  - Anomalies of great vessels, especially persistence of the vena cava cranialis sinistra
  - Abnormal lung lobation

- Gastro-intestinal:
  - Esophageal atresia
  - TE-fistula
  - Anal atresia with fistula
  - Malrotation
  - Common mesentery
  - Omphalocele
  - Meckel’s diverticulum

- Urinary:
  - Malformation of kidneys
  - False implantation of the ureters into the bladder
  - Bladder obstruction

- Limbs:
  - Agenesis/hypoplasia of radius/thumb
  - Postaxial hexadactyly
  - Duplication of thumb/big toe

- Radiologic:
  - Rib and vertebral anomalies

VIII. Congenital malformations uncommon to autosomal chromosome aberrations 1/4

- CNS:
  - Anencephalus
  - Exencephalus
  - Iniencephalus
  - Otocephalus
  - Acephalus

- Face:
  - Oblique clefts
  - Median cleft face
  - Duplication of nose
  - Lip pits

- Gastro-intestinal:
  - Atria of jejunum/ileum
  - Total situs inversus
  - Gastrochisis

- Urinary:
  - Exstrophy of bladder
  - Exstrophy of cloaca

- Limbs:
  - Peromelia
  - Amelia
  - Phocomelia
  - Ectrodactyly, split hand/feet
  - Arthrogryposis
  - Unlar or fibular ray defects

- Others:
  - Acardius, severely disorganized twin
  - Conjoined twins
  - Teratoma
  - Sirenomelia

- Radiologic:
  - Skeletal dysplasias
  - Spondylo-costal dysplasias
  - Short limb dwarfism

IX. Examples for specific combination

- inv dup(22)(pter-q11):
  - Anal atresia
  - Coloboma
  - (preauricular malformations, TFPVR, renal)
  - Trisomy 18:
  - Esophageal atresia
  - Radial hypoplasia
  - (CHD, renal, ..)

- Deletion of (11)(p13):
  - Aniridia
  - Nephroblastoma
  - (Ambiguous male genitalia)

- Deletion of (13)(q14-qter):
  - Agenesis of first rays (fingers, toes)
  - Ambiguous male genitalia
  - Anal atresia
  - Microphthalmia

X. Growth in chromosome aberrations

- Growth retardation very frequent.
- Constant for many aberrations.
- Postnatal retardation by far more frequent than intrauterine growth retardation.
- Prediction of adult height using normal tables often gives false values.
- Delayed bone maturation very frequent.
- Children with chromosome aberrations often undergo late or/and diminished puberty and continue to grow longer than chromosomally normal children (even up to 23 - 25 years).
- Growth hormone deficiency is rare.
- Growth hormone therapy may improve growth in chromosome aberrations.
- Normal growth: e.g.
XI. Course in adolescents and adults

- Growth: Continues longer than in normal adolescents.
- Puberty: Absent/diminished/late.
- Mental: Tendency of the IQ to fall with development: advancing age; standstill of this tendency in young adults, but early senescence.
- Premature ageing:
  - Very common in autosomal chromosome aberrations.
  - Starts at about 18 - 25 years.
  - Premature greying and loss of hair.
  - Osteoporosis.
  - Atrophic skin changes.
- Further fall of IQ.
- Alzheimer-like loss of intellectual capacity, memory etc.
- Rise of death curve after ca. 35 years of age.

XII. Puberty and fertility

- X chromosome aberrations: Puberty diminished and delayed; infertility or grossly reduced fertility.
- Autosomal aberrations:
  - Very variable!
    - Normal puberty occurs regularly in a few aberrations, e.g. many ring chromosomes, inv dup(15), cat eye syndrome (inv dup 22)
    - Diminished and delayed puberty in many aberrations
    - No puberty at all is not infrequent in both sexes, more often found in males, and especially in those with severe mental retardation
  - Females: primary amenorrhea and secondary amenorrhea (after primary oligomenorrhea) are frequent
  - Fertility:
    - Most patients with chromosome aberrations have no Offspring.
    - This is due to gonadal hypoplasia and dysfunction, mental deficiency, lack of sexual interests and non-aggressivity (in autosomal aberrations).
- Fertility is more common in females: Occasionally in trisomy 21, autosomal rings, del(18)(q21), trisomy 8 mosaicism, inv dup(22)(pter-q11), small autosomal duplications [e.g. dup(18p)].
- Offspring < 1/2 unbalanced.

XIII. Behavioural peculiarities in patients with chromosome aberrations

- The majority of special chromosome aberrations are associated with distinct personality traits.
- Patients with normal or near-normal intelligence: Frequent observations:
  - Non aggressive
  - Limited self-confidence
- Strong tendency towards psychosis under stress and unfavourable circumstances.
- Social quotient (SQ) often higher than intelligence quotient (IQ).
- Deficit mainly in intellectual functions.
- Specific:
  - Turner syndrome:
    - Poor room cordination
    - Poor in calculation, good in languages
    - Strong in unfavourable situations; good at school
  - Klinefelter syndrome:
    - Poor concentration
    - Low frustration tolerance
    - Poor performance at school

XIV. Chromosome aberrations and tumours

- Specific associations:
  - Deletion of 13q14 segments and osteosarcoma
  - Deletion of 11p13 segments and Wilms tumour
  - Deletion of 5q15/21 segments and intestinal polyposis
  - 45,X/46,XY or various Y mosaics and gonadoblastoma
- Non-random associations:
  - Early childhood leukaemia in trisomy 21
  - Various tumours in trisomy 8 mosaicism
XV. Potential pitfalls in karyotype-phenotype correlations

- Incorrect determination of karyotypes (chromosomes, breakpoints).
- Incomplete, unprecise or incorrect clinical data.
- Chance.

XVI. Increasing size towards the centomere does not alter the dysmorphic pattern of partial trisomy in:
- 3q, 4p, 6q, 7q, 9p, 10p, 10q, 16p, 18q, 20p

XVII. Partial trisomy and tetrasomy for similar segment

- extra isochromosome 5p, 8p, 9p, 12p, 18p, Xq
- inv dup chromosome: 14q12, 15q12, 21q11, 22q11, Xp21, Xq26, Yp11, Yq12
- Clinical pictures very similar
- Tetrasomy less viable than trisomy, often mosaics
- Tetrasomy tends to go along with more severe mental retardation and limited survival as compared to trisomy of the same segment

XVIII. Strong or less strong selection for cytogenetic examinations?

- Strong selection: Chromosome examination only performed in cases with high suspicion of a chromosome aberration.
- Requires continuous activities of very experienced clinical geneticists and cytogeneticists and an optimal flow of information/good collaboration with clinicians.

- Advantage: saves a lot of resources (health insurance costs); concentration to effective and interesting work.
- Disadvantage: misses some highly interesting and unusual cases where unexpectedly a chromosome aberration was found; unemployment.

XIX. Prenatal Cytogenetic Diagnosis

- 1984: Chorionic villus chromosome examination.
- 2000:
  - More prenatal than postnatal chromosome examinations
  - 15% of western European pregnancies controlled
  1. 60% for advanced maternal age
  2. Wish
  3. Abnormal ultrasound findings
  4. Abnormal AFP screening result
  5. Previous child with chromosome aberration
- Up to now decrease in live births with chromosome aberration is balanced by increasing mean maternal age (for trisomy 21 and sex chromosome aberrations); true decrease of liveborn with trisomy 13 & 18, triploidy and 4p- (due to ultrasound).

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