

# Leukaemia Section

## Mini Review

### t(4;17)(q12;q21)

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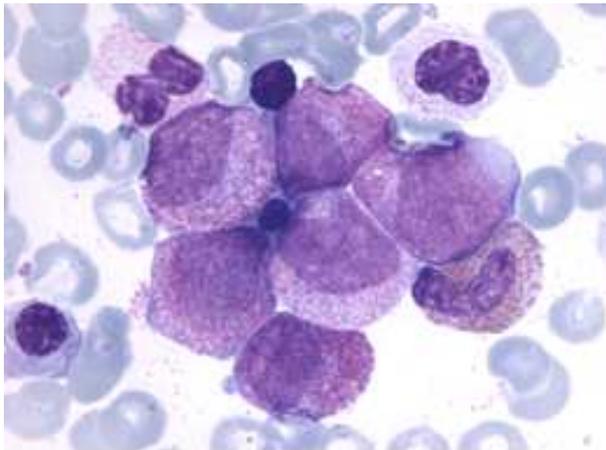
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## Clinics and pathology

### Disease

Juvenile myelomonocytic leukemia.



Morphology of JMML. Bone marrow smears were stained with May-Grünwald-Giemsa and shown at 1000-fold magnification. Bd=band, Bl=myelomonoblast Eb=erythroblast, Mc=myelocyte, Mo=monocyte, Pm=promyelocyte, Se=segmented neutrophilic granulocyte.

### Epidemiology

So far 1 case known.

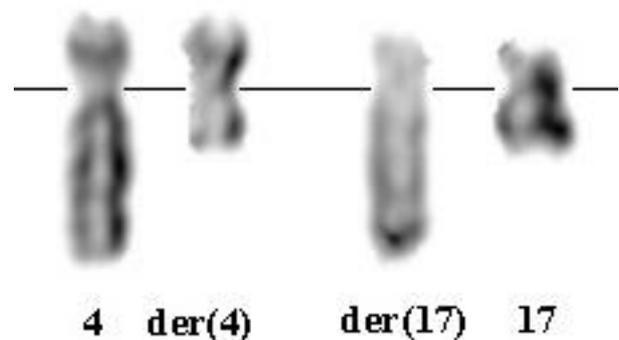
### Evolution

At relapse: 45,XY,-4,t(4;17)(q12;q21), add(5)(p15),del(7)(q22), -9, -16, -17, +3mar[19]/46,XY[5]

### Prognosis

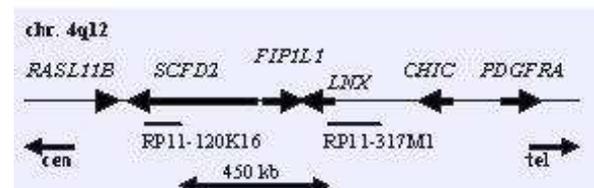
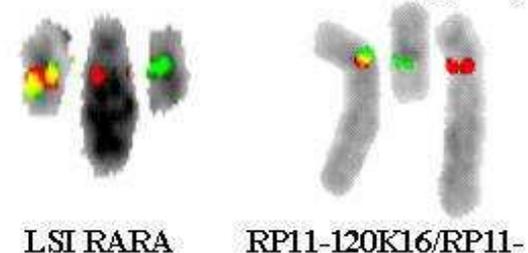
Patient succumbed after two SCT.

## Cytogenetics

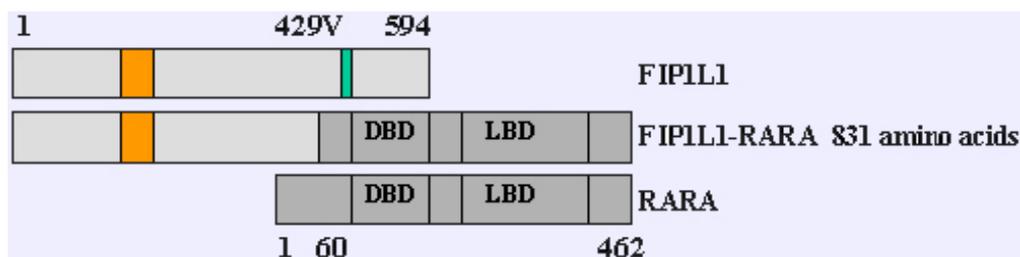


Partial GTG-banded karyotype of t(4;17)(q12;q21).

17 der(17) der(4) 4 der(4) der(17)



FISH analysis using probe LSI RARA DC resulting in a fusion signal on chromosome 17 band q21, with a split 5'RARA red signal on der(17) and a 3'RARA green signal on der(4) (left panel). FISH analysis narrowing the 4q12 breakpoint to the proximity of FIP1L1 by using 4q12 specific BAC probes RP11-120K16/RP11-317M1 with a fusion signal on chromosome 4 band q12, with RP11-120K16 hybridizing to der(4)(green) and RP11-317M1 hybridizing to der(17)(red) (right panel).



FIP1L1: Conserved FIP domain; RARA; DBD DNA binding domain, LBD ligand binding domain.

### Variants

In APL 17q21 RARA frequent rearrangement in: t(15;17)(q22;q21), fused with PML; in related translocations, rarely observed, involve a common breakpoint in 17q21, within RARA, fused with different partners, in: t(11;17)(q23;q21), fusion with PLZF, t(5;17)(q35;q12), fusion with NPM1, in t(11;17)(q13;q21), fusion with NUMA and in dup(17)(q12q21), fusion with Stat5b. In myeloproliferative disease CEL 4q12 FIP1L1 rearrangement: fusion to PDGFRA due to 800 kb interstitial deletion.

## Genes involved and Proteins

### FIP1L1

**Location:** 4q12

#### Protein

FIP1L1 is a subunit of the cleavage and polyadenylation specific factor (CPSF) complex that binds to U-rich elements via arginine-rich RNA binding motif and interacts with poly(A)polymerase (PAP).

### RARA

**Location:** 17q21

#### Protein

Wide expression; nuclear receptor; binds specific DNA sequences: HRE (hormone response elements); ligand and dimerization domain; role in growth and differentiation.

## Results of the chromosomal anomaly

### Hybrid gene

#### Description

In-frame fusion of exon 15 of FIP1L1 to exon 3 of RARA

#### Transcript

5' FIP1L1 - 3' RARA and 5' RARA - 3' FIP1L1

### Fusion protein

#### Description

The fusion mRNA would encode a 832 amino acids FIP1L1/RARA chimeric protein containing the 428

amino-terminal amino acids of FIP1L, including the FIP homology domain and 403 carboxyl-terminal amino acids of RARA, including the DNA and ligand binding domains, with replacement of FIP1L1 amino acid 429 (Valine) and RARA amino acid 60 (Threonine) into an Alanine.

### Oncogenesis

All known chimeric RARA fusion proteins provide additional homodimerization motifs, promoting formation of chimeric homodimers and thereby removing requirement of RXR for RARA to bind DNA. The homodimerization ability of RARA fusion proteins is critical for leukemic transformation. Recently, it was shown in a murine system that retroviral transduced FIP1L1/PDGFR $\alpha$  mediated transformation in vitro and in vivo, is FIP1L1 independent and results from disruption of the autoinhibitory JM domain of PDGFR $\alpha$ . However, observations using retroviral transduced FIP1L1/PDGFR $\alpha$  and FIP1L1/PDGFR $\alpha$  with an N-terminal deletion of the FIP1L1 moiety showed differences with respect to cytokine-independent colony formation and activation of multiple signalling pathways in human primary hematopoietic precursor cells, indicating that FIP1L1 contributes to FIP1L1/PDGFR $\alpha$  resulting in a myeloproliferative phenotype. Therefore the function of the FIP1L1 moiety remains to be resolved.

## To be noted

We report on reciprocal FIP1L1/RARA fusion transcripts resulting from a novel t(4;17)(q12;q21) in a case of juvenile myelomonocytic leukemia (JMML). JMML is a pediatric myeloproliferative disease (MPD), characterized by proliferation of granulocytic and monocytic lineages. 17q12 RARA was demonstrated to be involved in t(15;17)(q22;q21), resulting in a PML/RARA fusion transcript. PML/RARA t(15;17) is the hallmark of acute promyelocytic leukemia (APL), characterized by a differentiation arrest of abnormal promyelocytes. Variant rearrangements involving 17q21 RARA in APL and APL-like (APL-L) disease are PLZF/RARA t(11;17)(q23;q21), NPM1/RARA t(5;17)(q35;q21), NUMA/RARA t(11;17)(q13;q21), STAT5b/RARA der(17) and t(3;17)(p25;q21). 4q12 FIP1L1 is fused to PDGFR $\alpha$  as a result of a del(4)(q12q12) in myeloproliferative disorder CEL.

## References

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*This article should be referenced as such:*

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