

# Leukaemia Section

## Short Communication

### t(1;9)(q24;q34) RCSD1/ABL1

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#### Abstract

Review on t(1;9)(q24;q34) translocation, with data on clinics, and the genes involved.

#### Keywords

chromosome 1; chromosome 9; ABL1; RCSD1; B-cell acute lymphoblastic leukemia

#### Clinics and pathology

##### Disease

B-cell precursor ALL with expression of CD79a+, CD19+, CD10+, TdT (Mustjoki et al., 2009; Collette et al., 2015 )

##### Epidemiology

12 cases with an ABL1 split by FISH and/or RCSD1/ABL1 fusion, aged 5 to 40 years (median age 15 years); male predominance (8 males and 4 females); among them 1 with ABL1-positive biphenotypic ALL in which, however, the partner gene has not been identified.

##### Cytology

Hyperleukocytosis (WBC range at diagnosis 24 to 470 x 10<sup>9</sup>, median 110 x 10<sup>9</sup>); bone marrow blasts ranging from 58 to 95%.

##### Prognosis

Poor response to induction chemotherapy and in addition to induction failure, a high risk of relapse including patients after bone marrow transplantation. B-ALL patients with the RCSD1/ABL1 fusion are characterized by susceptibility to tyrosine kinase inhibitor therapy

(imatinib, dasatinib, ponatinib) and may achieve transient clinical effects as well as long time remission (Table 1; Data from De Braekeleer et al., 2013; Perwein et al., 2016) )

#### Cytogenetics

See Figure 1.

#### Genes involved and proteins

##### ABL1 (*v-abl* Abelson murine leukemia viral oncogene homolog 1)

##### Location

9q34.12

##### DNA/RNA

The ABL gene is approximately 225 kb in size and is expressed as a 7-kb mRNA transcript, with alternatively spliced first exons, exons 1b and 1a, respectively, spliced to the common exons 2-11. Exon 1b is approximately 200 kb 5-prime of exon 1a.

##### Protein

The 145-kD ABL protein is classified as a nonreceptor tyrosine kinase.

When the N-terminal region of the ABL protein is encoded by exon 1a, the protein is believed to be localized in the nucleus, while when encoded by exon 1b, the resulting N-terminal glycine would be myristylated and thus postulated to direct that protein to the plasma membrane.

	Sex/ Age	Diagnosis	WBC (x10 <sup>9</sup> /L)	PB/BM blasts (%)	Genetic testing results	Therapy	Survival (months)
1	M/15	BAL	122	95/ NA	46,XY,t(1;9)(q23.3~q25;q34) <i>ABL1</i> -rearranged (FISH)	Chemotherapy	10 died
2*	M/11	B-ALL	6	47/92	46,Y,add(X)(p22),t(1;9)(q24;q34) <i>ABL1</i> -rearranged (FISH) <i>RCSD1-ABL1</i>	Chemotherapy, BMT, relapsed 2 years after the initial treatment	97
3	40/M	B-ALL	24	34/80	46,XY,t(1;9)(q24;q34) <i>RCSD1-ABL1</i>	Chemotherapy + dasatinib, BMT Chemotherapy + dasatinib/ imatinib at relapse	66
4	F/18	B-ALL	110	87/ 92	t(1;9)(q24;q34) <i>ABL1</i> -rearranged (FISH) <i>RCSD1-ABL1</i>	NA	NA
5	F/15	B-ALL	348	NA/NA	46,XX,t(1;9)(q24;q34) <i>RCSD1-ABL1</i>	Chemotherapy, BMT at 4, 35 and 84 months following relapse.	84 died
6	M/31	B-ALL	146	90/NA	46,XY,t(1;9)(q23;q34),inv(2)(p21q 33) Developed: 45,XY,t(1;9),inv(2),t(5;16)(q33;q2 4), dic(18;20)(p11;q11) and 46,XY,t(1;9),inv(2),t(5;16),dic(18;2 0),der(19)t(17;19)(q21;p13),+21 <i>RCSD1-ABL1</i>	Chemotherapy, transient clinical effects with imatinib, and dasatinib.	6.5 died
7	M/16	B-ALL	48	NA/ NA	<i>RCSD1-ABL1</i> identified by RNA- sequence analysis	NA	NA
8	M/18	B-ALL	470	52/58	46,XY,t(1;9)(q24;q34) <i>RCSD1-ABL1</i>	No compliance to therapy	12+
9	M/6	B-ALL	108	NA/ NA	46,XY,t(1;9)(q23;q34) <i>ABL1</i> -rearranged <i>RCSD1-ABL1</i>	Chemotherapy + imatinib, poor response to chemotherapy	1
10	F/26	B-ALL	26	84/86	46,XX,t(1;9)(q24;q34) <i>RCSD1-ABL1</i>	Chemotherapy +dasatinib, BMT, relapse Chemotherapy +ponatinib, BMT Ponatinib monotherapy, relapse	25 died
11	F/15	B-ALL	251	45/NA	46,XX,t(1;9)(q24;q34) <i>IKS deletion</i>	Chemotherapy + dasatinib BMT	8 died
12	M/15	B-ALL	69	71/95	46,XY,t(1;9)(q31?;q34) <i>RCSD1-ABL1</i>	Chemotherapy + imatinib 2 months after relapse: sustained clinical remission	163

Abbreviations: WBC., white blood cells; PB., peripheral blood; BM., bone marrow; M., male; F., female; ALL., acute lymphocytic leukemia; \* at relapse; BMT., bone marrow transplantation.

1. Gonzales et al., 2004; 2. De Braekeleer et al., 2011; 3. Mustjoki et al., 2009; 4. Zamecnikova et al., 2010; De Braekeleer et al., 2013; 5. De Braekeleer et al., 2011; 6. Inokuchi et al., 2011; 7. Roberts et al., 2012; 8. De Braekeleer et al., 2013; 9. Roberts et al., 2014; 10. Collette et al., 2015; 11. Kamran et al., 2015; 12. Perwein et al., 2016

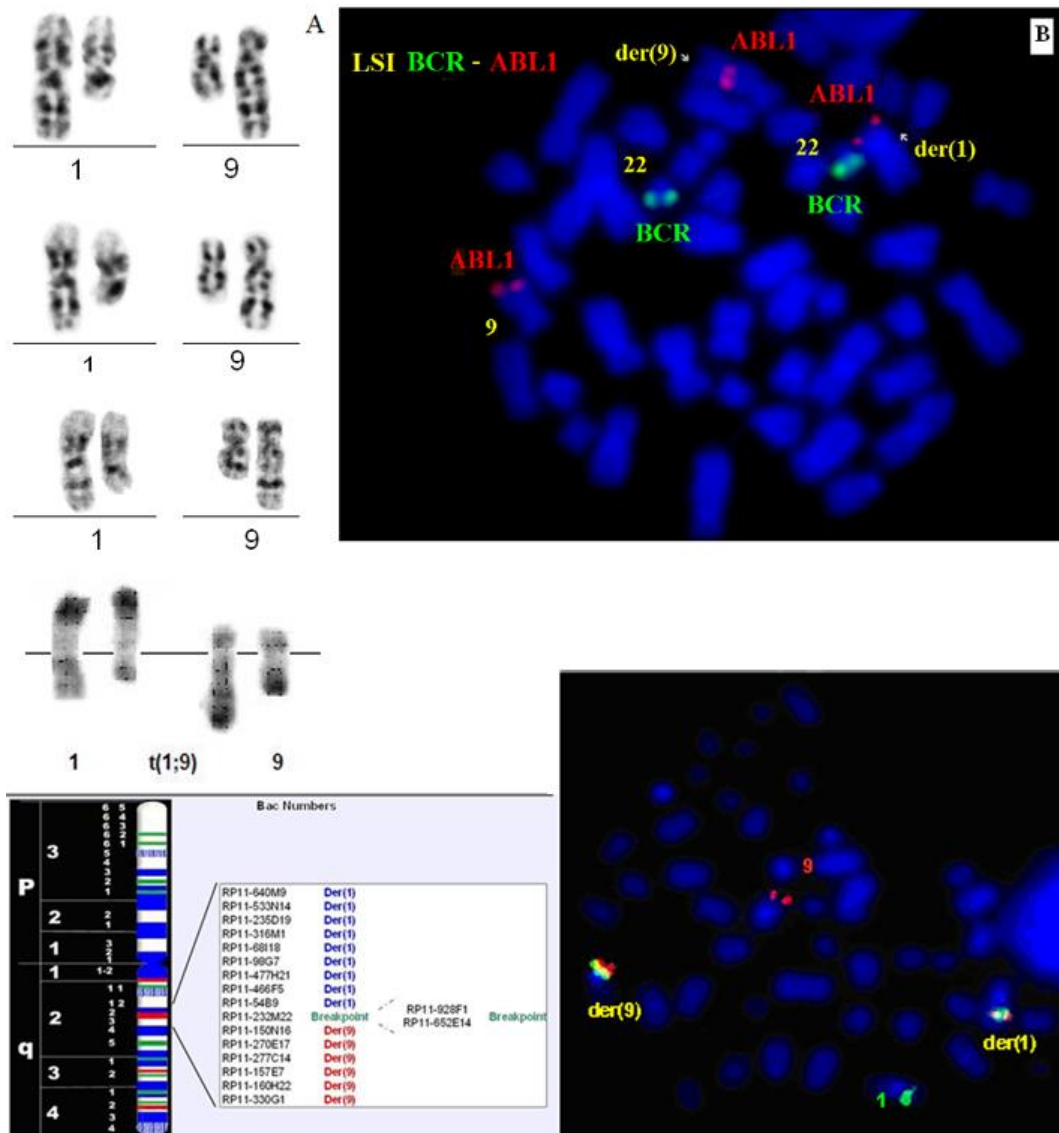


Figure 1. Top - courtesy Adriana Zamecnikova and Soad al Bahar: (A) Partial G-banded karyotypes showing the t(1;9)(q24;q34) and fluorescence in situ hybridization with LSI BCR/ABL1 (Vysis/Abott, US) probe showing the split of the ABL1 signal (red). A: Dual-color FISH using RP11-83J21 (labeled in spectrum orange) and RP11-232M22 (labeled in spectrum green) showing two fusion genes. FISH, fluorescence in situ hybridization. B: Probes. Bottom - courtesy Etienne De Braekeleer and Marc De Braekeleer: R-banded karyotype showing the t(1;9)(q24;q34) translocation. Dual-color FISH using RP11-83J21 (labeled in spectrum orange). Probes and RP11-232M22 (labeled in spectrum green) showing two fusion genes. FISH, fluorescence in situ hybridization. LSI bcr/abl dual extra-signal (ES) color probe (Abbott, Rungis, France) and BAC Probes. RP11-83J21 (chromosome 9) and RP11-232M22, RP11-928F1, RP11-138P14, RP11-652E14, RP11-64D9 (chromosome 1). All the probes that were used to find the breakpoint on der(1).

## RCSD1 (RCSD domain containing 1)

### Location

1q24.2

### DNA/RNA

Eyers et al. (2005) cloned for the first time the human RCSD1, which they called CAPZIP. A 416-amino acid protein was deduced and they calculated a molecular mass of 44.5 kD. Northern blot analysis resulted in a major 3.4-kb transcript and a minor 7-kb transcript that is highly expressed in skeletal muscle and weakly in cardiac muscle. CAPZIP is detected in several lymphoid organs, including

spleen, thymus, peripheral blood leukocytes, lymph node, and bone marrow.

### Protein

Eyers et al. (2005) found many properties of rabbit Capzip. It interacted specifically with the F-actin capping protein CapZ. This protein was phosphorylated by : MAPKAPK2 and SAPK3 (MAPK12), on ser108 by SAPK3 and SAPK4 (MAPK13) and on ser68, ser83, and ser216 by JNK1 alpha-1 (MAPK8) in vitro. This team also found that stress induced by hyperosmotic shock and anisomycin, a protein synthesis inhibitor, stimulated the phosphorylation of CAPZIP in human cell lines

and induced the dissociation of CAPZIP from CAPZ in Jurkat human T cells. This phenomenon may regulate the ability of CapZ to remodel actin filament.

## Result of the chromosomal anomaly

### Hybrid gene

#### Description

RCSD1/ABL1. In-frame fusions of first three exons of RCSD1 to ABL1 exon 4 to 11 and alternatively spliced RCSD1/ABL1 consisting of the first two exons of RCSD1 fused to exon 4 of ABL1 lacking RCSD1 exon 3 (Mustjoki et al., 2009).

#### Detection

FISH detection.

### Fusion protein

#### Description

The RCSD1/ABL1 fusion gene encode the tyrosine kinase domain of ABL1. The chimeric protein contains part of the SH2 domain of ABL1, the SH1 domain (that has tyrosine kinase function), the 3 nuclear localization signal domains, the 3 DNA-binding regions and the F-actin-binding domain. Notably, unlike most of the previously described chimeric genes involving ABL1 that fuse with exon 2 of ABL1 (containing ABL1 exons 2 and 3), the RCSD1/ABL1 protein contains only a truncated ABL1 protein starting from the exon 4-encoded region, therefore retains only a part of the ABL SH2 domain (with tyrosine kinase function), predicting its association with ALL rather than chronic myeloid leukemia (Mustjoki et al., 2009; De Braekeleer et al., 2013; Collette et al., 2015).

#### Oncogenesis

The RCSD1 gene, which codes a protein kinase substrate, CapZIP (CapZ-interacting protein), is found in immune cells, splenocytes and muscle. It is possible that the interaction between CapZIP and CapZ affects the cell ability to remodel actin filament assembly. CapZIP is phosphorylated when cells are exposed to various cellular stresses, which activate the kinase cascade. The interaction between CapZIP and CapZ would be lost when CapZIP is phosphorylated. So, RCSD1 would be involved in the remodeling of the actin cytoskeleton, which is an important step in mitosis. The probable formation of the ABL1-RCSD1 fusion gene could result in an alteration of the cellular function by affecting the cytoskeleton regulation, which could be an important step in leukemogenesis.

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