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Leukaemia Section
Short Communication

t(2;9)(q37;q34)

Purvi M Kakadia, Stefan K Bohlander

Center for Human genetics, Philipps University Marburg, Baldingerstrasse, Marburg, Germany (PMK, SKB)

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Identity

Other names
INPP5D/ABL1 fusion
SHIP1/ABL1 fusion

Clinics and pathology

Disease

c-ALL

Epidemiology

Only one case known to date, a 18-year-old female patient.

Clinics

Immature lymphoid blast population CD19+, CD10+, with no co-expression of myeloid markers.

Treatment

Treated with Imatinib; a complete remission (CR) was obtained. Continued CR after bone marrow transplantation (Follow-up: 15 months).

Cytogenetics

Cytogenetics morphological

Normal karyotype. This translocation would be hard to detect using conventional cytogenetics.

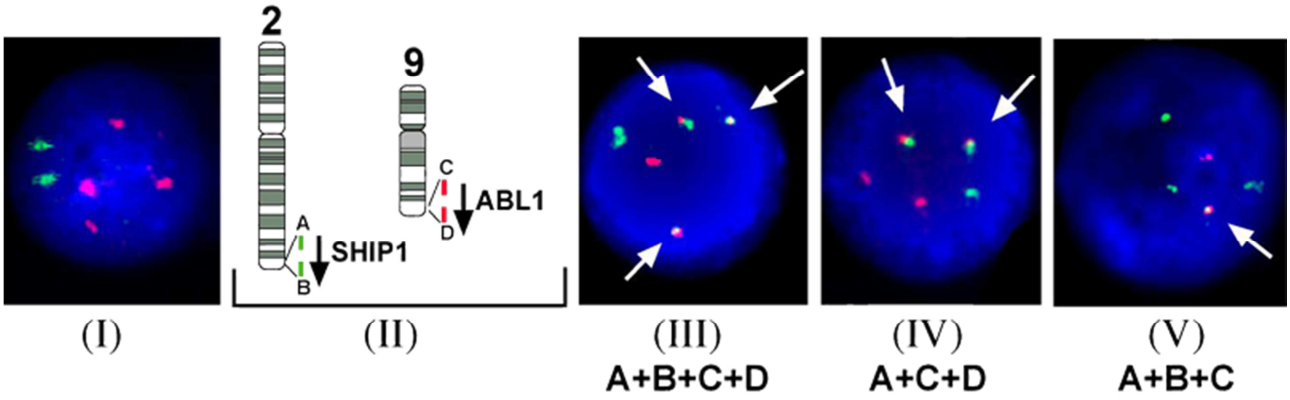

Figure 1: FISH analysis: (I) Interphase nuclei showing four FISH signals for ABL1 (orange) with a commercial BCR/ABL-DCDF probe. **(II)** Schematic diagram showing the position of the BAC clones corresponding to the 3' and 5' portions of the SHIP1 and ABL1 genes, with the color scheme used for the fluorescent labelling of the SHIP1/ABL1 DCDF probes. The BAC clones for SHIP1 were labelled with FITC and those for ABL1 were labelled with Texas Red. (SHIP1 clones: A: RP13-497I2 and B: RP13-916J2; ABL1 BAC clones: C: RP11-57C19 and D: RP11-835J22). **(III-V)** Interphase FISH demonstrating the presence of three fusion signals using the SHIP1-ABL1-DCDF probes **(III)**, two SHIP1-ABL1 fusion signals, when SHIP1-ABL1 fusion specific probes were used **(IV)** and presence of one reciprocal ABL1/SHIP1 fusion using the ABL1-SHIP1 fusion specific FISH probe **(V)** in the patient sample. With all three probe combinations one normal copy of each the SHIP1 and ABL1 locus was also confirmed. The probes used for the hybridization are indicated below each image. The fusion signals (yellow) are indicated by arrows.

Cytogenetics molecular

ABL1 rearrangement observed in interphase cells but not on metaphase chromosomes by FISH using commercial BCR-ABL-DCDF probes (Abbott). FISH using SHIP-ABL-DCDF FISH probes showed two fusion signals indicating the SHIP1-ABL1 fusion and one fusion signal for the reciprocal fusion on interphase cells. The rearrangement was not observed on the metaphase chromosomes, possibly because the malignant cells did not go into mitosis.

Genes involved and proteins

INPP5D

Location
2q37.1

Note
Other names: SHIP, SHIP1, SIP-145, hp51CN.

DNA/RNA
Transcript variant 1: NM_001017915.1; 26 exons, 4928 bp mRNA.
Transcript variant 2: NM_005541.3; 26 exons, 4925 bp mRNA.
There is also an INPP5D transcript variant described with 29 exons in the Ensembl database (INPP5D-201 ENST00000359570).

Protein
Proteins: Variant 1 contains 1189 aa and Variant 2 contains 1188 aa.

Domains: An N-terminal SH2 domain, an inositol phosphatase domain and two C-terminal protein interaction domains (Figure 3, upper box).
Expression: The expression of SHIP1 is restricted to hematopoietic cells.
Localization: Cytosol and plasma membrane; the localization of SHIP1 (cytosol vs. plasma membrane) is regulated by its SH2 domain which mediates interaction with tyrosine phosphorylated receptors.
Function: SHIP1 is a phosphatase, which hydrolyzes the 5-phosphates from phosphatidylinositol (3,4,5)-trisphosphate (Ptdins(3,4,5)P3; PIP3) and inositol-1,3,4,5 tetrakisphosphate (Ins(1,3,4,5)P4; PIP4) (Damen et al., 1996), thereby negatively regulating the PI3K (phosphoinositide 3-kinase) pathway.
The PI3K pathway is part of many important signalling pathways and regulates key cellular functions such as survival, proliferation, cell activation and cell migration (Krystal, 2000; Ward and Cantrell, 2001; Ward, 2006).
SHIP1 regulates these important cellular functions by controlling PIP3 levels and Ras activity following cytokine stimulation (Batty et al., 1985; Damen et al., 1996).
Homology: Belongs to the inositol-1,4,5-trisphosphate 5-phosphatase family.
Contains an SH2 domain.

ABL1

Location
9q34

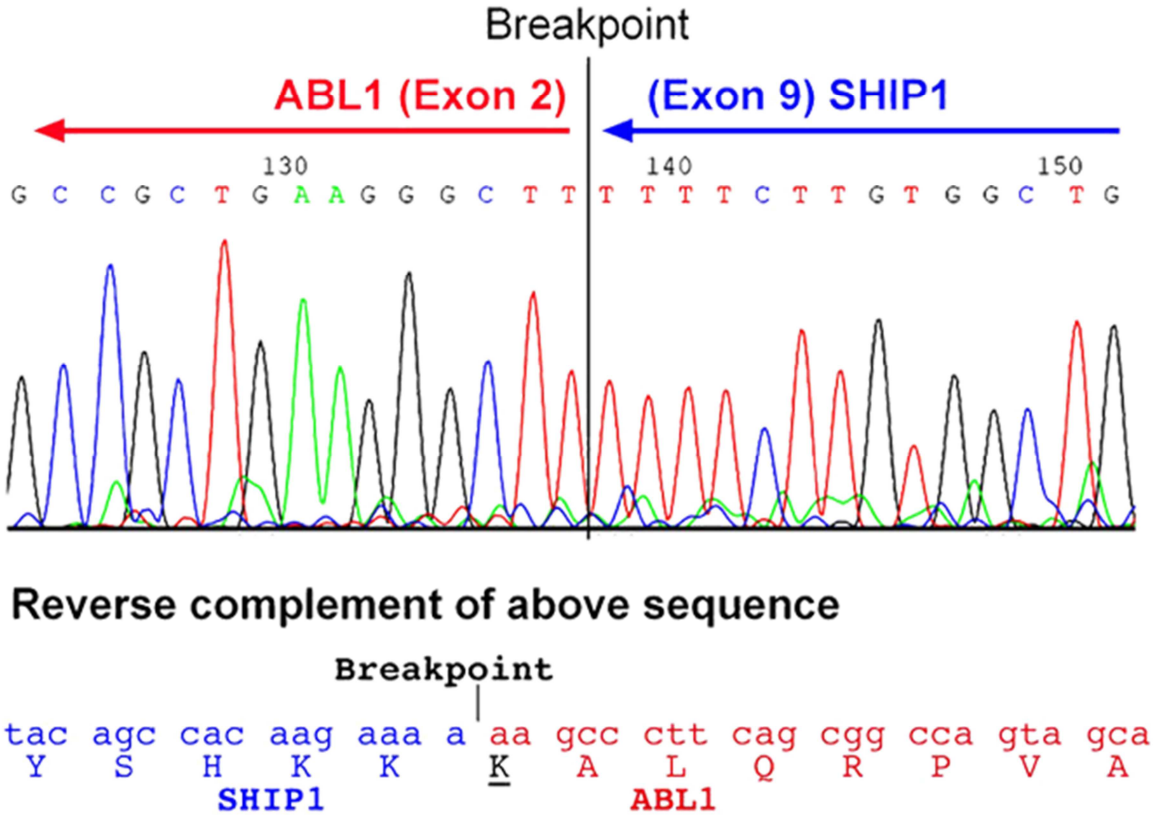

Figure 2: Partial sequence of the PCR product showing an in-frame fusion of SHIP1 with ABL1.

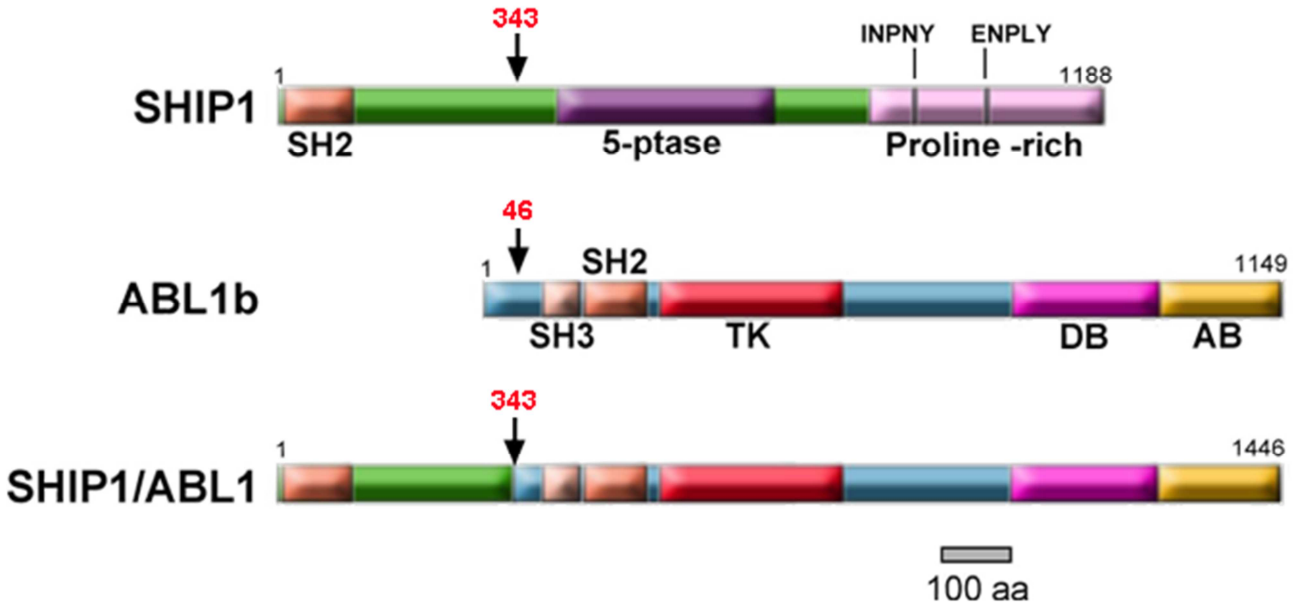

Figure 3: The upper two diagrams show the SHIP1 and the ABL1 proteins and the lower diagram depicts the SHIP1/ABL1 fusion protein. The arrows indicate the breakpoints in the individual proteins; numbers indicate amino acid positions. SH2: Src homology-2 domain; SH3: Src homology-3 domain; 5-ptase: Inositol 5-phosphatase domain; INPNY and ENPLY: Target sequences for the phospho tyrosine binding domains of other proteins; TK: Tyrosine kinase domain; DB: DNA binding domain; AD: Actin-binding domain.

Result of the chromosomal anomaly

Hybrid gene

Transcript

Only SHIP1-ABL1 fusion transcript was detected. The reciprocal ABL1-SHIP1 fusion transcript was not detected.

Detection

The SHIP1-ABL1 fusion transcript can be detected by 5' SHIP1 forward primer (bp 997-1015): 5'-TTGCTGCACGAGGGTCCTG-3' and 3' ABL1 reverse primer (bp 1474-1454): 5'-TCTCCAGACTGTTGACTGGCG-3' resulting in 477 bp PCR product.

Fusion protein

Description

The fusion protein leads to the constitutive activation of the ABL1 tyrosine kinase facilitated by the homo-di- and homo-heteromerization of the fusion protein via the dimerization domain within the N-terminal SHIP1 portion contained in the fusion protein.

Oncogenesis

Constitutive activation of ABL1 tyrosine kinase activity and possibly inactivation of the putative tumor suppressor function of SHIP1.

References

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