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Short Communication

t(2;9)(q12;q34) RANBP2/ABL1

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Abstract

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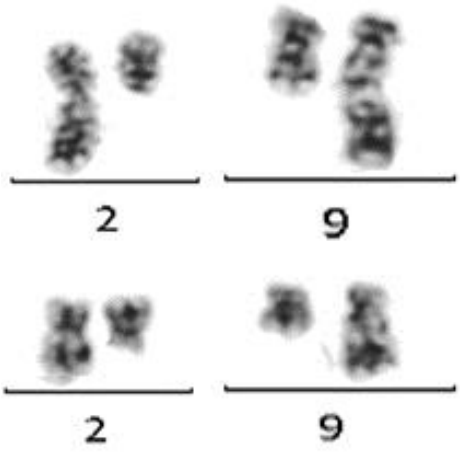
Review on t(2;9)(q12;q34), with data on clinics, and the genes involved.

Keywords: chromosome 2; chromosome 9; RANBP2; ABL1



GTG banding showing chromosomes 2 and 9 and the derivatives der(2) and der(9).

Clinics and pathology

Disease

Pre-B acute lymphoblastic leukemia

Epidemiology

Two cases reported: a 15year-old male (Roberts et al., 2012; Roberts et al., 2014) and a 21-month girl (Braekeleer et al., 2015).

Evolution

Alive 23 months after diagnosis in complete remission for one case, unknown for the other.

Cytogenetics

The t(2;9)(q12;q34)involves the RANBP2 and ABL1 genes. This fusion was first identified by RNA-sequencing in a boy with B-cell ALL (Roberts et al., 2012).

Cytogenetics morphological

t(2;9)(q12;q34) is identified by banding cytogenetics.

Cytogenetics molecular

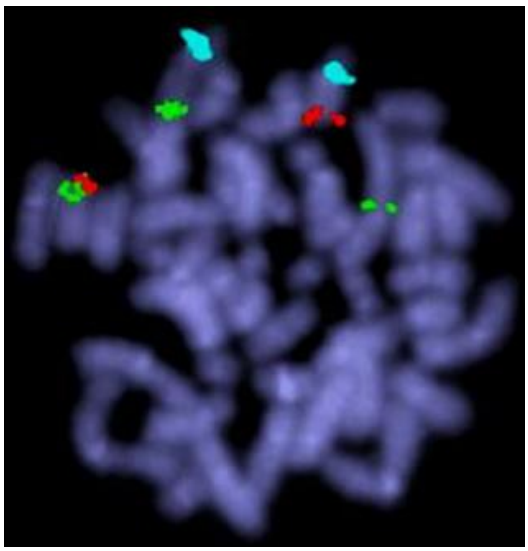
FISH with a BCR-ABL probe showed 3 ABL signals. To determine the position of the breakpoints on chromosome 2, BACs located in bands 2q12.1 to 2q14.2 were used as probes in FISH experiments.
A split signal on der(2) and der(9) was found with RP11-622D1, RP11-347H10, RP11-259O12, RP11-348G16 and RP11-953L12. These BAC clones overlap the RANBP2 gene and allow refinement of the breakpoint to a 25kb region covering the 5' end and the first three exons of RANBP2 (figure BAC).

Genes involved and proteins

RANBP2 (RAN binding protein 2)

Location

2q12.3



FISH with BACs RP11-953L12 (spectrum green, located in 2q12 and containing RANBP2) and RP11-83J21 (spectrum orange, located in 9q34 and containing the 3' part of ABL1) and CEP9 (in aqua) showing one fusion signal on der(2). No fusion is detected on der(9) because RP11-83J21 does not cover the 5' part of ABL1.

DNA/RNA

The RANBP2 (alias NUP358) gene contains 31 exons, spanning 66 kb. One major transcript with several alternative splicing variants is known.

Protein

The protein has 3324 amino acids and is the largest component of nuclear pore complexes. It contains an N-terminal leucine-rich region, four RAN binding domains, eight zinc-finger motifs, a SUMO E3 ligase region and a C-terminal cyclophilin A-like domain. A detailed assessment of its functions is available elsewhere in the Atlas (Di Cesare E, Lavia P. RANBP2 (RAN binding protein 2. http://AtlasGeneticsOncology.org/Genes/RANBP2ID483.html).

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

Location

9q34.12

DNA/RNA

The ABL1 gene, spanning a 230kb region at band 9q34, includes the 5' alternative first exons 1b and 1a and ten common exons numbered from 2 to 11. Alternative splicing using exons 1b and 1a gives rise to mRNA of 7 and 6 kb, respectively.

Protein

The ABL1 protein has three SRC homology (SH) domains called SH1, SH2 and SH3, of which SH1 that has tyrosine kinase function.

The SH2 and SH3 domains are involved in protein-protein interactions, which regulate the tyrosine kinase activity; they are necessary for signal transduction function. The ABL1 protein has also three nuclear localization signal domains and three DNA binding regions and an F-actin binding domain.

Result of the chromosomal anomaly

Hybrid gene

Description

The 3' region of ABL1 is translocated on the 5' region of RANBP2 on the der(2) and the 3' region of RANBP2 is translocated on the 5' region of ABL1 on der(9).

Detection

FISH detection.

Fusion protein

Description

The fusion protein retains the leucine-rich domain, including a leucine zipper, located at the N-terminal of RANBP2 and the tyrosine kinase domain of the ABL1 protein.

Oncogenesis

The leucine-rich region of RANBP2 is predicted to mediate homo-oligomerization of the fusion protein, leading to the activation of the tyrosine kinase of ABL1.

To be noted

Two other genes are known to fuse to RANBP2 and generate in-frame transcripts. These are ALK in inflammatory myofibroblastic tumor (Li et al., 2013;Ma et al., 2003), diffuse large B-cell lymphoma (Lee et al., 2014) and myeloid neoplasm (Lim et al., 2014;Maesako et al., 2014;Rottgers et al., 2010) and FGFR1 in myeloproliferative neoplasm (Gervais et al., 2013). In all cases, the fusion protein includes the leucine zipper portion of RANBP2 and the tyrosine kinase domain of the partner protein, leading to its activation.

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