inv(2)(p23q13) RANBP2/ALK / t(2;2)(p23;q13) RANBP2/ALK

Eul-Ju Seo

Department of Laboratory Medicine, University of Ulsan College of Medicine, Asian Medical Center, Seoul, Korea

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Abstract

The fusion of the anaplastic lymphoma receptor tyrosine kinase (ALK) gene in myeloid malignancies is extremely rare. The RANBP2-ALK fusion of inv(2)(p23q13)/t(2;2)(p23;q13) combined with monosomy 7 has been reported in a few patients diagnosed with acute myelomonocytic leukemia or juvenile myelomonocytic leukemia.

Keywords
RANBP2, ALK, monosomy 7, myelomonocytic leukemia

Identity

The inv(2)(p23q13) is an example of two variants involving ALK gene at 2p23 and RANBP2 gene at 2q13, inv(2) and t(2;2). The RANBP2/ALK fusion combined with monosomy 7 is associated with myeloid malignancies. This chromosomal rearrangement has also been observed in inflammatory myofibroblastic tumors (IMT).

Disease

Myeloid lineage: acute myelomonocytic leukemia, juvenile myelomonocytic leukemia

Phenotype/cell stem origin

Three cases of acute myelomonocytic leukemia (AML-M4), two cases of juvenile myelomonocytic leukemia (JMML).

Epidemiology

Five cases reported to date: 3M/2F; age 3.5-75 years (median 16 years).

Clinics

The five patients with inv(2)(p23q13) or t(2;2)(p23;q13) were two women (31, 75 years) and one 16 year-old male with acute myelomonocytic leukemia, and two boys (3.5, 8 years) with juvenile myelomonocytic leukemia.

The median WBC was 85.3 x 10^9/L (range, 55.6-143.6 x 10^9/L) and median monocyte count was 27 x 10^9/L (range, 20-55 x 10^9/L).
Cytology
Bone marrow: marked hypercellularity, granulocytic hyperplasia with leukemic blasts of myelomonocytic morphology.
Immunohistochemistry for ALK protein: strong staining of the nuclear membrane in leukemic cells.

Prognosis
In four cases, early relapse after 1 to 6 months; in two cases, early death after 2 and 14 months. Two pediatric patients were alive at 6 and 8 years after stem cell transplantation.

Cytogenetics

Cytogenetics morphological
Four out of five cases showed inv(2)(p23q13), and one case of JMML had t(2;2)(p23;q13). Interestingly, the monosomy 7 abnormality was observed in all cases, while it has not yet been reported in IMT cases.

Additional anomalies
Monosomy 7 (100%).

Genes involved and proteins

ELL
Location
2p23
Protein
1620 amino acids; 177 kDa; receptor tyrosine kinase.

RANBP2
Location
2q12.3
Protein
3224 amino acids; 358 kDa; large RAN-binding protein that immunolocalizes to the nuclear pore complex; E3 SUMO-protein ligase which facilitates SUMO1 and SUMO2 conjugation by UBE2I. Involved in facilitation of protein import and export, sumoylation of protein cargoes, intracellular trafficking, and energy maintenance.
Result of the chromosomal anomaly

**Hybrid gene**

**Description**
5' RANBP2 - 3' ALK.

**Transcript**
In-frame fusion transcript between RANBP2 exon 18 and ALK exon 20 in all cases.

**Fusion protein**

**Description**
1430-amino acid RANBP2-ALK fusion protein; The first 867 N-term amino acids of RANBP2 fused to the 563 C-term amino acids of ALK (i.e. the leucine-rich domain, including the leucine zipper, of RANBP2 and the entire cytoplasmic portion of ALK with the tyrosine kinase domain).

**Expression / Localisation**
Nuclear membrane.

**Oncogenesis**

RANBP2 protein contains an N-terminal 700-residue leucine-rich region predicted to mediate homo-oligomerization of the RANBP2-ALK oncoprotein, leading to the activation of the ALK kinase catalytic function.

**References**


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