

Leukaemia Section

Short Communication

t(2;11)(q31;p15) NUP98/HOXD13

t(2;11)(q31;p15) NUP98/HOXD11

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Identity

Note

t(2;11)(q31;p15) is an example of a variant translocation involving NUP98 gene at 11p15 which is fused with HOXD13 gene at 2q31.

This fusion produces a chimeric protein with leukemogenic activity. t(2;11)(q31;p15) is associated with myeloid malignancies.

Clinics and pathology

Disease

t(2;11)(q31;p15) is a rare but nonrandom translocation, reported in de novo acute myeloid leukemia (AML) as well as therapy related myelodysplastic syndrome/therapy related acute myeloid leukemia (t-MDS/t-AML), and one case of chronic myeloid leukemia in blast crisis (CML-BC).



Partial ideogram and G-banded karyotypes showing t(2;11)(q31;p15); arrows indicate breakpoints.

Phenotype/cell stem origin

Mostly AML-M4; bone marrow displaying monocytic features; AML-M6 in one case.

Epidemiology

Generally the incidence of NUP98 rearrangements in leukemia is difficult to estimate probably 1-2% of AML cases.

The t(2;15)(q32;p15) is rare; around 8 cases in literature; reported in male and female with 1:1 ratio; Infants under the age of a year; children (10-15 years) as well as adults (59-62 years); over-representation in Asian race in particular Japanese.

It has been shown that NUP98/11p15 is a frequent target for chromosomal rearrangements following chemotherapies with DNA topoisomerase II inhibitors. Interestingly, there are at least three infants leukemia with NUP98-HOXD13 gene fusion. It has been suggested that a high intake of certain diets rich in flavonoids during pregnancy increases the risk of infant leukemia due to the inhibition effect on topo II activity. It is worth to mention that in one infant, the NUP98-HOXD13 gene fusion was demonstrated retrospectively in neonatal blood spot. This provides strong evidence that the fusion is a prenatal event.

Clinics

Peripheral blood; High white cell counts (WBC) with elevated monocytes; low platelets;

Bone Marrow: Hypercellular marrow with monocytic differentiation;

Immunophenotypes; Cell surface marker expression included CD13, CD14, CD33, CD34, HLA-DR, CD11b, CD65.

Prognosis

Due to rarity of t(2;11) leukemia, it is difficult to determine the prognostic significance of this translocation in leukemia.

However, all de novo t(2;11) AML achieved remission, while patients with t-AML progressed rapidly. Generally, NUP98 gene fusion in leukemia predicts poor clinical outcome.

Cytogenetics

Cytogenetics morphological

Sole Anomaly; t(2;11)(q31;p15) was a sole anomaly in 5/8 cases.

Additional anomalies

Trisomy 8 in one case; balanced translocations in one case; in a CML-BC case t(2;11)(q31;p15) was secondary to Ph chromosome.

Variants

t(2;11;9)(q31;p15;q22)/NUP98-HOXD13 fusion in one case.

Genes involved and proteins

HOXD13 (homeobox D13)

Location

2q31.1

DNA/RNA

HOXD11 and HOXD13 genes, located on chromosome 2q31, are member of a large family of developmental homeobox genes. Homeobox genes encode evolutionarily conserved transcription factors that appear to be involved in body plan formation and embryonic development, and also play a critical role in limb development.

HOXD11 (homeobox D11)

Location

2q31.1

DNA/RNA

See above.

NUP98 (nucleoporin 98kDa)

Location

11p15

DNA/RNA

NUP98 gene, located on chromosome 11p15, encodes a 98-KD protein a component of nuclear pore complex (NPC). NUP98 is found in the nucleoplasmic and cytoplasmic domains of the NPC, and functions as a transport co-factor of RNA and protein between the nucleus and cytoplasm. In addition, NUP98 appear to be involved in mitotic spindle formation and in cell cycle progression. Haploinsufficiency of NUP98 gene has been shown to cause premature separation of sister chromatids leading to severe aneuploidy.

In leukemia, there are at least 29 different partner genes fused with NUP98, 50% of which are homeobox genes. Different genes are likely associated with different leukemic phenotypes.

Result of the chromosomal anomaly

Hybrid gene

Description

5'-NUP98-HOXD13-3' fusion is the oncogenic product of the t(2;11); exon 12 of NUP98 gene is fused in-frame with exon 2 of HOXD13 gene.

Fusion protein

Description

NUP98 fusion gene encodes a chimeric protein which is the amino terminal portion of NUP98 protein fuses the carboxyl portion of the partner gene HOXD13. The fused protein acts as an aberrant transcription factor. Several studies have demonstrated that NUP98-HOXD13 fusion protein blocks differentiation of hematopoietic precursor cells, and has aberrant self-renewal capacity.

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