

Leukaemia Section

Short Communication

t(5;11)(q35;q12) NSD1/FEN1

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Abstract

Review on t(5;11)(q35;q12) NSD1/FEN1, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

Acute monocytic leukemia (AML-M5b)

Epidemiology

Four cases of acute myeloid leukemia with t(5;11)(q35;q12-13) are reported in the literature: two acute myeloblastic leukemia with differentiation (AML-M2) (Wang et al., 2006; de Oliveira et al., 2007), one acute myelomonocytic leukemia (AML-M4) (Itoh et al., 1999) and one acute monoblastic leukemia (AML-M5) (Leverger et al., 1988). No molecular characterization was performed in these cases but the NSD1 gene was shown not to be involved by fluorescent in situ hybridization in the AML-M2 case reported by Wang et al. (2006).

Clinics

A 37-year-old man seen because of throat infection resistant to antibiotics, persistent fever and dyspnea.

Treatment

Induction therapy and several salvage therapies failed to achieve complete remission followed by bone marrow transplantation.

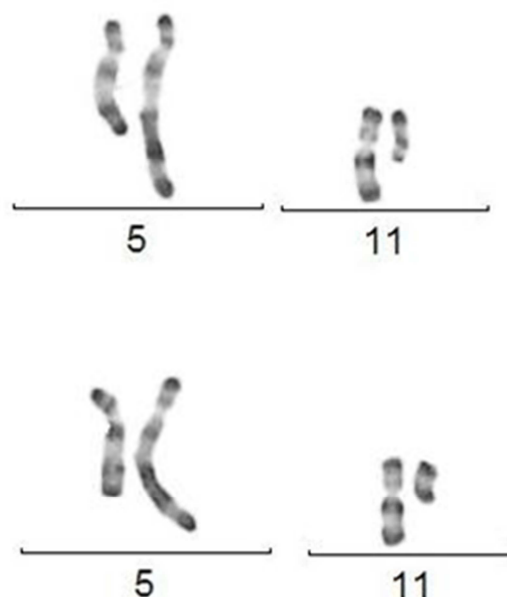
Evolution

Patient alive in complete remission 35 months following bone marrow transplantation.

Cytogenetics

Note

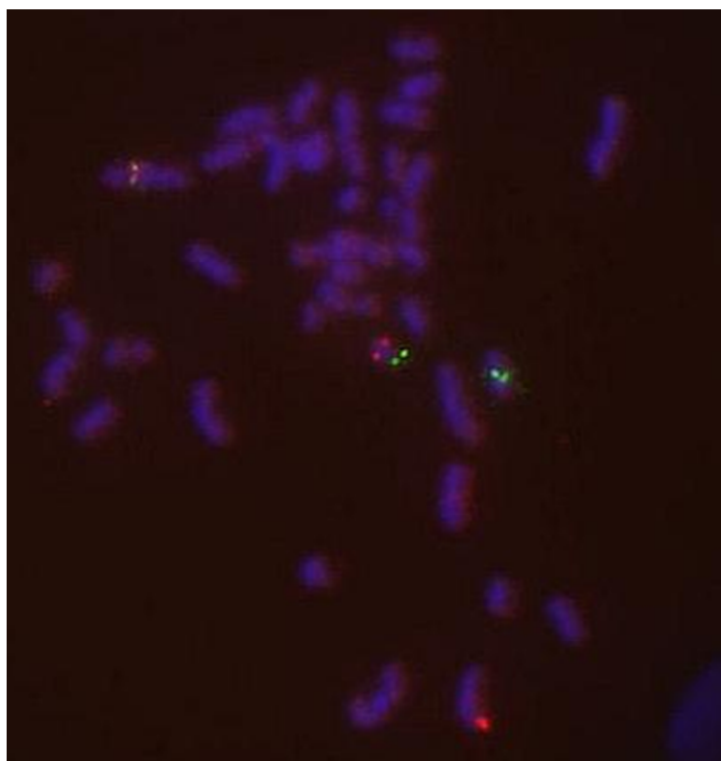
The t(5;11)(q35;q12) involves two genes of which one, the NSD1 gene, has been already shown to form a fusion gene with NUP98 in the t(5;11)(q35;p15.1) (Jaju et al., 2001).



RHG banding showing chromosomes 5 and 11 and the derivatives der(5) and der(11).

Cytogenetics morphological

t(5;11)(q35;q12) is identified by banding cytogenetics.



FISH with BACs RP11-99N22 (spectrum orange, located in 5q35 and containing NSD1) and RP11-467L20 (spectrum green, located in 11q12 and containing FEN1) showing co-hybridization.

Cytogenetics molecular

To determine the position of the breakpoints on chromosomes 5 and 11, BACs located in the bands of interest were used as probes in FISH experiments.

Analysis with RP11-99N22 showed that one signal hybridized to the normal chromosome 5, and the other split and hybridized to both der(5) and der(11).

FISH with overlapping BACs identified a very small region of breakage in RP11-467L20. Analysis with RP11-467L20 showed that one signal hybridized to the normal chromosome 11, and the other split and hybridized to both der(11) and der(5).

Co-hybridization with both BAC clones showed two fusion signals. RP11-99N22 contains the NSD1 gene and RP11-467L20 the FEN1 gene.

Genes involved and proteins

NSD1

Location

5q35.3

DNA/RNA

The NSD1 gene contains 24 exons, of which 23 are coding, spanning 167 kb. Two alternative transcripts are known (Kurotaki et al., 2001).

Protein

The protein has 2696 amino acids and localizes to the nucleus. It contains a SET domain, 2 LXXLL motifs, 3 nuclear translocation signals, 4 plant homeodomain (PHD) finger regions, and a proline-rich region. The protein acts as a basic transcriptional factor and also as a bifunctional transcriptional regulator, capable of both negatively or positively influencing transcription, depending on the cellular context (Huang et al., 1998; Kurotaki et al., 2001).

FEN1

Location

11q12.2

DNA/RNA

The FEN1 gene contains 2 exons, of which a sole is coding, spanning 4 kb (Hiraoka et al., 1995).

Protein

The protein has 380 amino acids and localizes to the nucleus. It is a structure-specific nuclease with 5'-flap endonuclease and 5'-3' exonuclease activities involved in DNA replication and repair. It acts as a genome stabilization factor that prevents flaps from equilibrating into structures that lead to duplications and deletions and participates in telomere maintenance (Saharia et al., 2008; Zheng et al., 2011; Tsutakawa et al., 2011). It has been suggested that FEN1 is a tumor suppressor gene (Henneke et al., 2003).

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