t(6;9)(p23;q34) DEK/NUP214

Jean-Loup Huret

Genetics, Dept Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France (JLH)

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Identity

t(6;9)(p23;q34) G-banding (left): Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap Cytogenetics at the Waisman Center (top and middle top), Jean-Luc Lai (middle below), and Roland Berger (below); and R-banding - Courtesy Lucienne Michaux (top 2); and Courtesy Christine Pérot (bottom 2).
The translocation t(6;9)(p23;q34) results in the formation of a chimeric fusion gene: DEK (6q23) and CAN (9q34). CAN is a putative oncogene which may be activated by fusion of its 3’ end to other genes than DEK. One such recently reported gene is called SET and leads to expression of a SET/CAN fusion RNA. The t(6;9)(p21-22;q34) may be seen in either AML M2 or less frequently in M4 or MDS and acute myelofibrosis often in association with excess basophils. The t(6;9) is reported mostly in young adults. The prognosis of patients carrying the t(6;9) is unfavorable - Courtesy Georges Flandrin.

Clinics and pathology

Disease

Acute myeloid leukemias (AML) and myelodysplastic syndromes (MDS)

Phenotype/cell stem origin

Altogether, 191 cases are available: 110 cases extracted from the Mitelman database (Cases quick searcher + Molecular biology associations searcher), cases from Garçon et al., 2005, and cases from the largest study to date (69 cases) (Slovak et al., 2006).

The WHO/FAB classification was: M1-AML: 13% (25/191 cases), M2-AML: 34% (64/191), M1/M2-AML: 1% (2 cases), M4-AML: 24% (45/191), M5-AML: 2% (4 cases), M6-AML: 2% (3 cases), AML not otherwise specified (26 cases), refractory anemia with excess of blasts (RAEB): 7% (13/191), chronic myelogenous leukemia (CML): 2% (3 cases), other myelodysplastic and/or myeloproliferative syndrome: 2% (3 cases), acute basophilic leukemia: 1 case, unknown: 2 cases. Acute myeloid leukemia is often preceded by an episode of myelodysplastic syndrome. The t(6;9) may be secondary to toxic exposure; in some instances.

In the t(6;9), long-term (Sca1+/c-Kit+/lin- /Flk2-) hematopoietic stem cells (LT-HSC) appear to be the leukemia-initiating cells, while leukemia-maintaining cells represent a larger and phenotypically heterogeneous cell population (Oancea et al., 2010).

Epidemiology

The t(6;9) is found in about 1% of AMLs (0.9% in the series of 69 cases, with a repartition of 1.4% in children AMLs, and 0.7% in adult cases (Slovak et al., 2006)); from this study, median age was 23 years (range 2-66 years), with 30 children out of 69 cases (43%), a younger age than in AML in general. From 199 cases herein reviewed, the sex ratio is balanced: 1M/1F (100 male patients and 99 female patients).

Cytology

TdT +, HLA-DR, CD13, CD33, CD38, CD45 and CD117; frequent expression of CD9, CD15, CD34 Auer rods are frequently observed.

Blood data: a marked basophilia is frequent (found in 44% of the patients in Slovak et al., 2006). Granulocytic, megakaryocytic, or multilineage dysplasia was found in two third of adult cases in the same report.

Treatment

Allogeneic stem cell transplantation might be associated with better outcome (Slovak et al., 2006).
Overall survival in patients with t(6;9)(p23;q34) (adapted from Slovak et al., 2006): 31 children cases, 32 adult cases, compared with 174 young adult AML in the unfavorable risk cytogenetics subgroup.

Prognosis
Overall, 65% of patients, 71% of pediatric cases and 58% of adults, achieved complete remission (CR) (Slovak et al., 2006). Median survival is around 1 year (12.5 months in children, 14.4 months in adults, 13.5 months altogether). The 5 year overall survival was 28% in children and 9% in adults (see figure) (Slovak et al., 2006). Patients who achieved prolonged molecular remission had better outcome than patients with persistent DEK/NUP214 positivity (Garçon et al., 2005).

Genetics
Note
FLT3 internal tandem duplications was found in 69% of children cases and 73% of adult cases in one study (Slovak et al., 2006), and in 88% of adult cases in another study (Oyarzo et al., 2004). A third study grossly confirm this high incidence (Garçon et al., 2005).

Cytogenetics

Cytogenetics morphological
The t(6;9) may be overlooked.

Additional anomalies
The t(6;9) is the sole anomaly in 85% of 195 cases with available data, and in 83% of cases in the largest study (Slovak et al., 2006); recurrent, although rare, additional anomalies are the following: +8 (in 6 of 126 cases, 5%), +13 (in 3 of 126 cases, 2%), +21. A -7/del(7q) was found once, a t(9;22)(q24;q11) once.

Variants
A three way complex t(6;9;Var) has been found in 3 instances.

Genes involved and proteins

DEK
Location
6p23
Protein
375 amino-acids; DEK contains acidic domains (Asp/Glu-rich), a SAF/SAP box, a nuclear localisation signal; and other DNA binding domains. Highly conserved nuclear factor; chromatin remodeling protein, essential for heterochromatin integrity; DEK localizes preferentially at sites proximal to the promoters of expressed genes; acts as a repressor of transcription by interfering with histone acetyltransferases and as an activator of transcription by stimulating the binding of TFAP2A (the activator protein AP2-alpha) to its target DNA sequences; DEK introduces super-coils into circular DNA (in Oancea et al., 2010).

DEK is a regulator of stem and progenitor cells and is upregulated in a number of neoplasms (breast cancer, chronic lymphocytic leukemia, small cell lung carcinoma, Merkel cell carcinoma, melanoma, glioblastoma, retinoblastoma, cervical, and bladder cancers) (review in Riveiro-Falkenbach and Soengas, 2010); CEBPA and DEK coordinate activator myeloid gene expression (Koleva et al., 2012); DEK is an estrogen receptor alpha (ESR1) target gene (Privette


Lillington DM, MacCallum PK, Lister TA, Gibbons B. Translocation t(6;9)(p23;q34) in acute myeloid leukemia without myelodysplasia or basophilia: two cases and a review of the literature. Leukemia. 1993 Apr;7(4):527-31


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