Leukaemia Section

Short Communication

inv(11)(p15q23) NUP98/KMT2A

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Abstract

ABSTRACT
Review on inv(11)(p15q23) NUP98/KMT2A with data on clinics and on the genes involved.

KEYWORDS
Chromosome 11; inv(11); NUP98; KMT2A; myelodysplasia; acute myeloid leukemia; treatment related leukemia; acute lymphocytic leukemia; hairy cell leukemia; multiple myeloma; peripheral T-cell lymphoma.

Identity

Note
inv(11)(p15q23) is an heterogeneous disease, since a NUP98/KMT2A hybrid gene and fusion protein was detected in only 2 cases (Kaltenbach et al., 2010), whereas there was no evidence of involvement of KMT2A (MLL) in 2 other cases (Harrison et al., 1998). We herein review 21 cases of inv(11)(p15q23), most of them were not studied at the gene level. Was excluded in this review a case of precursor B-ALL where the inv(11)(p15q23) had instead a hidden MLL/ENL hybrid gene (Meyer-Monard et al., 2006). inv(11)(p15q23) has also been found in a case of breast adenocarcinoma, an adenocarcinoma of the ovary, a case of myxoid chondrosarcoma and a mesenchymal tumor, NOS of the corpus uteri, and are not herein reviewed (Mitelman database).

Clinics and pathology

Disease
inv(11)(p15q23) has been found in myelodysplasia, acute myeloid leukemia, treatment related leukemia, acute lymphocytic leukemia, hairy cell leukemia, multiple myeloma, peripheral T-cell lymphoma.

Phenotype/cell stem origin
There were 4 cases of myelodysplasia: a chronic myelomonocytic leukemia (CMMoL), a refractory anemia with excess blasts in transformation (RAEBt), and 2 myelodysplastic syndromes (MDS) not otherwise specified (NOS). (Bielorai et al., 2003; Harrison et al. et al., 1998; Inaba et al., 1988; Nebral et al., 2005).

There were 9 cases of acute myeloid leukemia: 2 cases of acute myeloblastic leukemia without maturation (FAB type M1), 3 cases of acute myeloblastic leukemia with maturation (FAB type M2), 1 case of acute promyelocytic leukemia (AML- M3), 2 cases of acute myelomonocytic leukemia AML- M4), and 1 case of acute myeloid leukemia, NOS (Casas et al., 2003; Harrison et al., 1998; Kaltenbach et al., 2010; Larramendy et al., 2002; Nebral et al., 2005; Odero et al., 2001; Xu et al., 2001; Yan et al., 2001).

There were 4 cases of treatment related myeloid malignancy: 1 RAEBt after Hodgkin disease and a
therapy-related RAEBt evolving toward AML-M5, and two FAB type M4 AML, one of which occurred after treatment of ALL. (Harrison et al., 1998; Nichols et al., 2002; Pui et al., 1989; Secker-Walker et al., 1998).

There was a case of childhood ALL (Heerema et al., 1992), a hairy cell leukemia (Haglund et al., 1994), a multiple myeloma (Sawyer et al., 2014), and a peripheral T-cell lymphoma (Lepretre et al., 2000).

The only 2 cases where NUP98/KMT2A fusion was ascertained were cases of M1 and M2 AMLs in a male patient aged 79 years and a female patient aged 30 years. Both patients died of disease. The inv(11)(p15q23) was the sole chromosome abnormality (Kaltenbach et al., 2010).

Epidemiology

Myeloid malignancy cases were 8 male and 9 female patients, median age was 40-44 years, range 2-79 years, with 5 children cases. Lymphoid malignancy cases sex ratio and ages were: 1M/3F, 17 yrs, 40 yrs, 53 yrs.

Prognosis

Data on survival is too scarce.

Cytogenetics

Cytogenetics morphological

In myeloid cases, the inv(11)(p15q23) was the sole anomaly, at least within a subclone, in thirteen cases, and was accompanied with +8 in two, -7/del(7q) in two, -5 in one, a complex karyotype in one case and with a t(15;17) in the M3-AML case. In lymphoid malignancy cases, the inv(11) was accompanied with del(6q) in two cases, and part of a complex karyotype in 2.

Genes involved and proteins

As said above, there was no evidence of involvement of KMT2A (MLL) in 2 cases (Harrison et al., 1998), whereas there was an in-frame fusion transcript between NUP98 and KMT2A in 2 patients (Kaltenbach et al., 2010). An hemizygous deletion of DDX10 and ATM was detected in one case (Nebral et al., 2005)

NUP98 (nucleoporin 98 kDa)

Location
11p15.4

Note
Data from Mohamed, 2016 follows:

DNA/RNA
NUP98 is one of several genes located in the imprinted gene domain of chromosome 11p15. Combined haploinsufficiency of NUP98 and RAEl has been shown to result in premature separation of sister chromatids, leading to severe aneuploidy. NUP98 plays roles in gene expression, mitotic spindle formation, and cell cycle progression.

NUP98 gene is fused to a large number of "partner genes" caused primarily by balanced translocations and inversions which are associated with a wide variety of hematological malignancies including AML and MDS (de novo and therapy related), CML-blast crisis, and pre T- ALL. To date, no NUP98 fusion gene has been described in B-cell malignancies. At least 30 different partner genes are reported to fuse with NUP98; 50% of which are homeobox genes. Approximately 10% of patients with NUP98 fusions have T-ALL; most commonly, these malignancies are associated with NUP98-RAP1GDS1 gene fusions. This suggests that different partner genes are associated with different leukemia, although such associations are rarely exclusive. Although NUP98 breakpoints in these translocations are variable located between introns 9 to 14, a chimeric transcript consisting of the 5' portion of NUP98 fused in-frame to the 3' portion of the partner genes is generated in all.

Protein

NUP98 gene encodes two alternatively spliced mRNA variants: NUP98 and NUP98-NUP96 that are cleaved to produce two distinct nucleoporins, NUP98 and NUP96. The NUP98 is a 98 kDa protein component of the nuclear pore complex (NPC) family which is involved in the trafficking of RNA and protein between the nucleus and cytoplasm. The NUP98 protein contains two partially characterized functional domains: a GLFG repeat region, which serves as a nuclear transport receptor docking surface, and a GLEBS domain, which mediates the interaction with the RAE1 mRNA nuclear export factor. Both domains are located within the N-terminal portion of NUP98. The chimeric NUP98 protein that results from translocations always retains the intact N-terminal GLFG repeats of NUP98 and the C-terminal domain of the partner protein. NUP96 is a scaffold component of the NPC (Mohamed, 2016).

KMT2A (myeloid/lymphoid or mixed lineage leukemia)

Location
11q23.3

DNA/RNA
37 exons, spanning about 120 kb; 13-15 mRNA

Protein

3969 amino acids, 431 kDa; Transcriptional regulatory factor. MLL is known to be associated with more than 30 proteins, including the core components of the SWI/SNF chromatin remodeling complex and the transcription complex TFID. MLL binds promoters of HOX genes through acetylation and methylation of histones. MLL is a major...
regulator of hematopoesis and embryonic development, through regulation of HOX genes expression regulation (HOXA9 in particular).

**Result of the chromosomal anomaly**

**Hybrid gene**

in-frame fusion transcript between exon 13 of NUP98 and exon 2 of KMT2A (Kaltenbach et al., 2010).

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*This article should be referenced as such:*