t(11;12)(p15;p13) NUP98/KDM5A

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Published in Atlas Database: January 2013

Online updated version: http://AtlasGeneticsOncology.org/Anomalies/t1112p15p13ID1428.html

DOI: 10.4267/2042/50195

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Clinics and pathology

Disease

Acute megakaryoblastic leukemia (AML-M7)

Note

Acute megakaryoblastic leukemia (AMKL) was so far divided into three subgroups: AMKL arising in patients with Down syndrome (DS-AMKL), AMKL with a t(1;22)(p13;q13) giving rise of a 5' OTT - 3' MAL fusion gene, and "other" AMKLs, non Down syndrome / non t(1;22).

Two new categories have recently been individualized from the subgroup "non Down syndrome / non t(1;22)"; the inv(16)(p13q24) CBFA2T3/GLIS2, and the t(11;12)(p15;p13) NUP98/KDM5A (Gruber et al., 2012; Thiollier et al., 2012). This t(11;12)(p15;p13) has been described earlier in a single case (van Zutven et al., 2006).

Epidemiology

From the two recent studies, t(11;12)(p15;p13) NUP98/KDM5A was found in about 10% of pediatric acute megakaryoblastic leukemia, excluding AMKLs occurring in Down syndrome patients; NUP98/KDM5A was detected in 8% (4 of 48) of pediatric cases. This chimeric transcript was not detected in adult AMKLs (Gruber et al., 2012). From another validation cohort of 22 non-DS pediatric AMKL, 9 DS AMKL, and 8 adult AMKL, a NUP98/KDM5A fusion was characterized in two patients (Thiollier et al., 2012).

Clinics

7 cases to date; data on age and sex are available in 5 cases (van Zutven et al., 2006; Gruber et al., 2012); there was 5 boys and no girl; sex ratio, so far, appears to be highly unbalanced, although the sample is very small; median age was 1 year 4 months (range: 1 year - 4 years).

Prognosis

Prognostic data available in only one case (van Zutven et al., 2006): the patient remained in complete remission for at least 5 years.

Cytogenetics

Cytogenetics morphological

Not visible with conventional banding techniques alone: misdiagnosed as add(11)(p15) and der(21)(t(11;21)(p15;p13), and chromosome 12 was cytogenetically normal by conventional banding techniques and only identified as a partner in this translocation after FISH in the first reported case (van Zutven et al., 2006). A complex karyotype was found in 4 of the 5 cases with data on chromosomes; the remaining case exhibited an apparently normal karyotype (van Zutven et al., 2006; Gruber et al., 2012).
Schematic representation of the fusion NUP98-KDM5A (previously named NUP98-JARID1A). From up to down: NUP98, JARID1A and the putative chimeric NUP98-JARID1A structure. FG-repeats: phenylalanine-glycine repeats; JMJ: Jumonji domains; ARID: AT-rich interaction domain; PHD: plant homeodomain fingers or LAP domains. The arrow indicates the position of the fusion (Laura JCM van Zutven and H Berna Beverloo).

**Genes involved and proteins**

**NUP98**
- **Location**: 11p15
- **Protein**: 920 amino acids; 97 kDa; contains repeated motifs (GLFG and FG) in N-term and a RNA binding motif in C-term. Nucleoporin: associated with the nuclear pore complex; role in nucleocytoplasmic transport processes.

**KDM5A**
- **Location**: 12p13
- **Note**: The gene was previously known as JARID1A.
- **Protein**: 1722 amino acids; 196 kDa; retinoblastoma binding protein 2. Lysine-specific histone 3 demethylase; involved in chromatin-regulation; can function as a transcriptional repressor. KDM5A-mediated histone H3 lysine 4 demethylation contributes to silencing of retinoblastoma target genes (Chicas et al., 2012). Dysregulation of KDM5A is associated with various human cancers: gastric cancer, lung cancer, breast cancer (Hou et al., 2012).

**Result of the chromosomal anomaly**

**Hybrid gene**
- **Description**: In-frame fusion of the first 13 exons of NUP98 to exons 28-31 of KDM5A.
- **Transcript**: 5’ NUP98 - 3’ KDM5A.
- **Detection**: FISH: BAC clones RP11-348A20 (NUP98) and RP11-283I3 (spanning KDM5A exon 11-31) colocalize.

**Fusion protein**
- **Description**: The NUP98/KDM5A fusion protein contains the Phe-Gly (FG) repeats of the N-terminal part of NUP98. The KDM5A (JARID1A) sequence starting with exon 28 still contains the sequence encoding the C-terminal PHD domain.
- **Oncogenesis**: Results in deregulation of HOXA genes through recruitment of the histone acetyltransferase CBP/p300 (Thiollier et al., 2012).
References


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