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Leukaemia Section
Short Communication

inv(16)(p13q24) CBFA2T3/GLIS2

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Clinics and pathology

Disease

Acute megakaryoblastic leukemia (AMKL)

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" AMLKs, i.e. 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).

Epidemiology

Fourteen patients with data on sex and age are available; median age at diagnosis was 1 year - 1 year 4 months (range 6 months - 4 years 7 months).

The inv(16)(p13q24) CBFA2T3/GLIS2 was found in about 30% of non-Down syndrome pediatric AMKL cases (in 13 of 48 cases in Gruber et al., 2012, and 7 of 22 cases in Thiollier et al., 2012. So far, none of the 36 adult AMKL cases under study contained the chimeric transcript.

One patient had a Down syndrome (case SJAMLM7018 in Gruber et al., 2012), which shows that DS-AMKL and inv(16)-AMLK categories are not mutually exclusive.

Prognosis

Subgroup of patients with a significantly worse overall survival at 5 years as compared to patients with AMKL that lacked this chimeric transcript (28% versus 42% in Gruber et al., 2012); fusion associated with treatment-refractory disease (Thiollier et al., 2012).

Cytogenetics

Cytogenetics morphological

This inversion of chromosome 16 is cryptic. The CBFA2T3/GLIS2 chimeric gene resulted from simple balanced inversions in three cases and from a complex rearrangement in one case (Gruber et al., 2012). A complex karyotype was found in 8 of the 12 cases with data on chromosomes; 2 remaining cases exhibited an apparently normal karyotype (Gruber et al., 2012).

Genes involved and proteins

GLIS2

Location

16p13.3

Protein

Kruppel-like zinc-finger protein. Transcription factor; repressor of the Hedgehog signaling pathway; repressor of the Wnt signaling pathway. GLIS2 has also been reported to localize to the primary cilium. A mutation GLIS2 has been linked to the development of nephronophthisis. Glis2 may act as a repressor of epithelial-mesenchymal transition (EMT) and EMT-related gene expression (Lichti-Kaiser et al., 2012).

CBFA2T3

Location

16q24.3

Protein

Member of the "ETO" family. Functions as a transcriptional repressor via interaction with corepressor complexes; do not directly bind DNA, but interacts with transcription factors such as BCL6, PLZF, GFI1, ZNF651 and ZNF652 (Kumar et al., 2010).

Result of the chromosomal anomaly

Hybrid gene

Description

5' CBFA2T3 - 3' GLIS2. Fusion between exon 10 of CBFA2T3 and exon 3 of GLIS2 in 6 cases (Gruber et al., 2012); fusion between exon 11 of CBFA2T3 and exon 3 of GLIS2 in 1 case (Thiollier et al., 2012); fusion between exon 11 of CBFA2T3 and exon 1 of GLIS2 in 1 case (Gruber et al., 2012).

Fusion protein

Description

Retains the three CBFA2T3 N-terminal nervy homology regions (NHR) that mediate protein interactions and the five GLIS2 C-terminal domains (ZnF) responsible for interaction with DNA and transactivation. The MYND (myeloid, nervy, and Deaf-1 domain, class of zinc finger domain reported to interact with the N-CoR repressor complex) domain of CBFA2T3 is lost.

Oncogenesis

This fusion between two transcriptional regulators results in aberrant expression of genes controlled either by CBFA2T3 or GLIS2 (Thiollier et al., 2012).

There is an homogenous gene expression signature including a strong expression of CD56. Among the differentially regulated genes are known targets of the Hedgehog pathway including BMP2, BMP4, GATA3, and CCND2. CBFA2T3/GLIS2 induces BMP signaling. Hedgehog and JAK-STAT pathways are significantly upregulated (Gruber et al., 2012; Thiollier et al., 2012). CBFA2T3/GLIS2 cells demonstrated enhanced self-renewal in vitro (Gruber et al., 2012). Aurora A kinase (AURKA) inhibitors can induce differentiation and inhibits proliferation of AMKL blasts (Thiollier et al., 2012).

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