t(1;12)(q21;p13) ETV6/ARNT

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t(1;12)(q21;p13) (AML, ALL; ARNT and ETV6; rare). Atlas Genet Cytogenet Oncol Haematol

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Abstract
Review on t(1;12)(q21;p13) ETV6/ARNT, with data on clinics, and the genes implicated.

Clinics and pathology

Disease
Myeloid and lymphoid malignancies

Note
Excluded from this review is a case of multiple myeloma (Lewis and MacKenzie, 1984).

Phenotype/cell stem origin
Two cases of acute lymphoblastic leukemia (ALL) have been described with a t(1;12)(q21;p13): an ALL not otherwise specified (NOS) in a female patient with no indication concerning the genes involved (Heerema et al., 2004), and a T-cell ALL (CD5+, CD7+, CD4-, CD8-) in a 2-year old boy, and with assessment of an ETV6/ARNT transcript (Otsubo et al., 2010). Three myeloid cases are available: a chronic myelogenous leukemia in blast crisis (BC-CML) in a female patient without molecular data (Palandri et al., 2009), a M2 acute myeloblastic leukemia (M2-AML) in a 5-year old boy with an ETV6/ARNT transcript (Otsubo et al., 2010), and a case of refractory anemia with excess blasts in transformation (RAEB-t) with total absence of erythroid precursors in bone marrow in a 64-year old male patient, where ETV6 may not be involved (Sánchez et al., 2000).

Epidemiology
In this small series, 2 of 3 cases, however, are found in pediatric patients.

Prognosis
Very scarce data: the BC-CML patient died 47 months after diagnosis.

Cytogenetics

Cytogenetics morphological
A del(7q) was found in an ALL case, a t(9;22)(q34;q11) in the BC-CML case, indeed, and the t(1;12) was the sole anomaly in the RAEB-t case.

Genes involved and proteins

Note
An ETV6/ARNT hybrid transcript has therefore been described in two cases: a case of T-ALL, and a case of M2-AML.
The breakpoint appears to be identical in the two cases: ETV6 exon 4 fused to the ARNT exon 2 (Otsubo et al., 2010), breakpoint after the 154 first amino acids in ETV6 and after the 8 first amino acids in ARNT (Salomon-Nguyen et al., 2000).

ARNT
Location
1q21
Protein
789 amino acids. ARNT is composed of a bHLH, basic helix-loop-helix domain, 2PAS, Per/ARNT/Sim homology domains, and a glutamine-rich transactivation domain. Transcription factor. Forms homodimers or heterodimers with AHR (7p21); mediates the cellular response to xenobiotic compounds such as environmental pollutants. Interacts with estrogen receptors (ER). ARNT is recruited to estrogen-responsive promoters, leading to increased ER transcription (reviews in Hankinson, 2004; Swedenborg and Pongratz, 2010).

ETV6
Location
12p13
Protein
452 amino acids. ETV6 is composed of a HLH domain responsible for hetero- and homodimerization in N-term, and an ETS domain responsible for sequence specific DNA-binding in C-term (binds to the DNA sequence 5’-CCGGAAGT-3’). Transcriptional regulator; tumor suppressor. Involved in bone marrow hematopoiesis.

Result of the chromosomal anomaly
Hybrid gene
Description
ETV6 exon 4 was fused in frame to the ARNT exon 2 (Otsubo et al., 2010).

Fusion protein
Description
Two fusion proteins are found as a result of this translocation. The ETV6/ARNT protein contains the 154 first amino acids, including the aminoterminal oligomerization domain of ETV6 and most of the ARNT protein, and is highly expressed in the leukemic cells of the patient (Salomon-Nguyen et al., 2000). The ARNT/ETV6 protein contains the first 8 amino acids of ARNT fused to the 298 carboxyl-terminal amino acids of ETV6 including its ETS DNA-binding domain. This protein is hardly expressed and is likely to be not involved in the malignant process (Salomon-Nguyen et al., 2000).

References
Heerema NA, Nachman JB, Sather HN, La MK, Hutchinson R, Lange BJ, Bostrom B, Steinherz PG, Gaynor PS, Uckun FM; Children’s Cancer Group..
Deletion of 7p or monosomy 7 in pediatric acute lymphoblastic leukemia is an adverse prognostic factor: a report from the Children's Cancer Group. Leukemia. 2004 May;18(5):939-47.


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