t(12;13)(p13;q12) ETV6/FLT3

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Abstract
Review on t(12;13)(p13;q12) ETV6/FLT3, with data on clinics, and the genes implicated.

Clinics and pathology

Disease
Acute lymphoblastic leukemia (ALL) and myeloid malignancies are described in cases of t(12;13)(p13;q12)

Note
The translocation t(12;13)(p13;q12) is molecularly heterogeneous:
The t(12;13)(p13;q12) with ETV6 and FLT3 involvement, herein described, was found in three cases of myeloproliferative neoplasm (MPN) with eosinophilia (Vu et al., 2006; Walz et al., 2011).
On the other hand, a t(12;13)(p13;q12) ETV6/CDX2 has been described in another case (Chase et al., 1999).
Finally, other cases of t(12;13)(p13;q12) without molecular ascertainment may or may not involve FLT3, CDX2, or even ETV6.

Epidemiology
All together, eleven cases of t(12;13)(p13;q12) were described.

Clinics
Three cases of t(12;13)(p13;q12) ETV6/FLT3 are reported:
A female patient aged 68 years, with a MPD with eosinophilia; she died 21 months after diagnosis.
A 60-year old man with a MPN with hypereosinophilia in accelerated phase; he died soon after diagnosis of infection and pancytopenia.
A 29-year old man who developed MPN with hypereosinophilia four weeks after autologous stem cell transplantation following a T-lymphoblastic lymphoma; he died 5 weeks after diagnosis of MPN.
Another case presents with a similar phenotype: a 49 year-old male patient, also with a MPN with eosinophilia; he died 11 months after diagnosis (and with a history of leukocytosis for last two years before diagnosis).
No molecular analysis was performed (Chiyoda et al., 1994).
The case with ETV6/CDX2 involvement was a 66 year old male patient with M1 acute myeloid leukaemia (AML); he died 40 months after diagnosis.
The six other known patients with a t(12;13)(p13;q12) were two children and one 17 year-old female patient with acute lymphoblastic leukemia (ALL) (Keene et al., 1987; Wlodarska et al., 1998; Heerema et al., 2000) and three adult patients with myeloid diseases (one refractory anemia with excess of blasts (RAEB) and two AMLs; one of which was a treatment-related AML (t-AML)) (Knapp et al., 1985; Tosi et al., 1998; Clavio et al., 2001).

Cytology
All three patients with ETV6/FLT3 had myeloproliferative neoplasm with eosinophilia.
**Cytogenetics**

**Cytogenetics morphological**
The t(12;13)(p13;q12) was the sole anomaly in six cases (three MPD with eosinophilia, one ALL, the RAEB and a M0-AML). The t(12;13)(p13;q12) was accompanied with -5 and -7 in the t-AML, and with major karyotypic anomalies (MAKA) in the CD10+ ALL in the 17 year-old female patient and the MPN in the 60 year-old male patient.

**Genes involved and proteins**

**Note**
In three patients, the ETV6/FLT3 implication was found (Vu et al., 2006; Walz et al., 2011). Following the first report, transgenic mice expressing ETV6-FLT3 were used (Baldwin et al., 2007).

**ETV6**

**Location**
12p13

**Note**
The ETV6 gene encodes a transcription factor frequently rearranged in myeloid and lymphoid leukemias.

**DNA/RNA**
The ETV6 gene spans a region of less than 250 kb at band 12p13.1 and consists of 8 exons. There are two start codons, one (exon 1a starting at codon 1) located at the beginning of the gene and another alternative (exon 1b starting at codon 43) upstream of exon 3.

**Protein**
The ETV6 protein (452 amino acids) contains two major domains, the HLH (helix-loop-helix) and ETS domains. The HLH domain, also referred to as the pointed or sterile alpha motif domain, is encoded by exons 3 and 4 and functions as a homo-oligodimerization domain.

**FLT3**

**Location**
13q12

**Note**
FLT3 is one of the most frequently mutated genes in hematologic malignancies, being found in about 30% of AML patients and rarely in ALL patients (Gilliland and Griffin, 2002; Stirewalt and Radich, 2003).

**DNA/RNA**
The FLT3 gene spans a region of 97 kb and consists of 24 exons.

**Protein**
The FLT3 gene is a member of the receptor tyrosine kinase subclass III family of genes. It encodes a protein structurally related to the receptors for platelet derived growth factor. Contains five immunoglobulin-like domains in the extracellular domain involved in protein-ligand interaction, a transmembrane domain, and an intracellular tyrosine kinase domain. Dimerization induces kinase domain activation, leading to the activation of intracellular signalling pathways. Expressed on early hemopoietic progenitor cells.

**Result of the chromosomal anomaly**

**Hybrid gene**

**Description**
Both ETV6/FLT3 and FLT3/ETV6 transcripts were detected. However, FLT3/ETV6 transcripts were out of frame. Various in frame fusion products of ETV6/FLT3 were found. Fusion of exon 5 of ETV6 5’ term to exon 14 of FLT3 3’ term (and exon 4 and 16 in one transcript) (Vu et al., 2006).

In-frame fusion genes were observed between exon 4 or 5 of ETV6 and exon 14 of FLT3 (Walz et al., 2011).
**Fusion protein**

**Description**
N-term Helix-loop-helix (HLH) oligodimerization domain of ETV6 fused to the transmembrane and tyrosine kinase domains of FLT3.

**Oncogenesis**
Constitutive tyrosine kinase activation of FLT3.

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