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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).
Expression of the fusion protein in the transgenic mice was found in spleen, bone marrow, thymus, and liver.
A significant increase in the number of CFU-GM, BFU-E, CFU-S and CFU-GEMM was produced.
Mice developed MPD with a high incidence but did not succumbed to leukemia (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.
The ETS domain, encoded by exons 6 through 8, is responsible for sequence specific DNA-binding and protein-protein interaction.
Transcriptional regulator; involved in bone marrow hematopoiesis.

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).

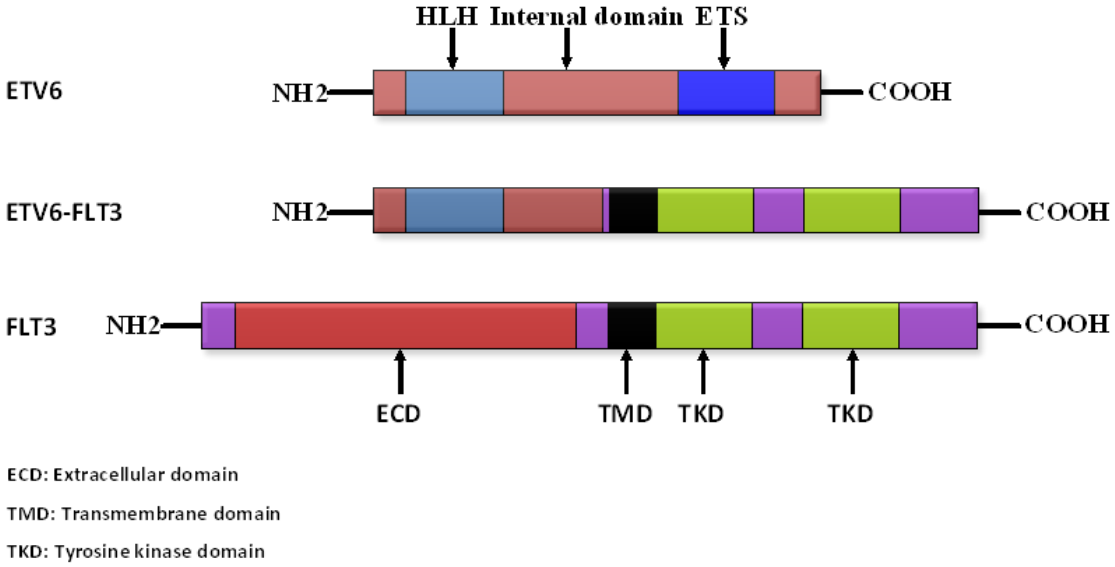
DNA/RNA
The FLT3 gene spans a region of 97 kb and consists of 24 exons.

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).



Schematic diagram of the ETV6, FLT3 and ETV6-FLT3 proteins.

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.

References

Knapp RH, Dewald GW, Pierre RV. Cytogenetic studies in 174 consecutive patients with preleukemic or myelodysplastic syndromes. Mayo Clin Proc. 1985 Aug;60(8):507-16

Keene P, Mendelow B, Pinto MR, Bezwoda W, MacDougall L, Falkson G, Ruff P, Bernstein R. Abnormalities of chromosome 12p13 and malignant proliferation of eosinophils: a nonrandom association. Br J Haematol. 1987 Sep;67(1):25-31

Rosnet O, Schiff C, Pébusque MJ, Marchetto S, Tonnelle C, Toiron Y, Birg F, Birnbaum D. Human FLT3/FLK2 gene: cDNA cloning and expression in hematopoietic cells. Blood. 1993 Aug 15;82(4):1110-9

Chiyoda S, Morikawa T, Takahara O. [Atypical chronic myeloproliferative disorder with translocation (12;13)(p13;q12) and tumor formation]. Rinsho Ketsueki. 1994 Dec;35(12):1355-60

Tosi S, Giudici G, Mosna G, Harbott J, Specchia G, Grosveld G, Privitera E, Kearney L, Biondi A, Cazzaniga G. Identification of new partner chromosomes involved in fusions with the ETV6 (TEL) gene in hematologic malignancies. Genes Chromosomes Cancer. 1998 Mar;21(3):223-9

Wlodarska I, La Starza R, Baens M, Dierlamm J, Uyttebroeck A, Selleslag D, Francine A, Mecucci C, Hagemeijer A, Van den Berghe H, Marynen P. Fluorescence in situ hybridization characterization of new translocations involving TEL (ETV6) in a wide spectrum of hematologic malignancies. Blood. 1998 Feb 15;91(4):1399-406

Chase A, Reiter A, Burci L, Cazzaniga G, Biondi A, Pickard J, Roberts IA, Goldman JM, Cross NC. Fusion of ETV6 to the caudal-related homeobox gene CDX2 in acute myeloid leukemia with the t(12;13)(p13;q12). Blood. 1999 Feb 1;93(3):1025-31

Heerema NA, Sather HN, Sensel MG, Lee MK, Hutchinson RJ, Nachman JB, Reaman GH, Lange BJ, Steinherz PG, Bostrom BC, Gaynon PS, Uckun FM. Abnormalities of chromosome bands 13q12 to 13q14 in childhood acute lymphoblastic leukemia. J Clin Oncol. 2000 Nov 15;18(22):3837-44

Mizuki M, Fenski R, Halfter H, Matsumura I, Schmidt R, Müller C, Grüning W, Kratz-Albers K, Serve S, Steur C, Büchner T, Kienast J, Kanakura Y, Berdel WE, Serve H. Flt3 mutations from patients with acute myeloid leukemia induce transformation of 32D cells mediated by the Ras and STAT5 pathways. Blood. 2000 Dec 1;96(12):3907-14

Clavio M, Gatto S, Beltrami G, Cerri R, Carrara P, Pierri I, Canepa L, Miglino M, Balleari E, Masoudi B, Damasio E, Ghio R, Sessarego M, Gobbi M. First line therapy with fludarabine combinations in 42 patients with either post myelodysplastic syndrome or therapy related acute myeloid leukaemia. Leuk Lymphoma. 2001 Jan;40(3-4):305-13

Gilliland DG, Griffin JD. The roles of FLT3 in hematopoiesis and leukemia. Blood. 2002 Sep 1;100(5):1532-42

Stirewalt DL, Radich JP. The role of FLT3 in haematopoietic malignancies. Nat Rev Cancer. 2003 Sep;3(9):650-65

Vu HA, Xinh PT, Masuda M, Motoji T, Toyoda A, Sakaki Y, Tokunaga K, Sato Y. FLT3 is fused to ETV6 in a myeloproliferative disorder with hypereosinophilia and a t(12;13)(p13;q12) translocation. Leukemia. 2006 Aug;20(8):1414-21

Baldwin BR, Li L, Tse KF, Small S, Collector M, Whartenby KA, Sharkis SJ, Racke F, Huso D, Small D. Transgenic mice expressing Tel-FLT3, a constitutively activated form of FLT3, develop myeloproliferative disease. Leukemia. 2007 Apr;21(4):764-71

Walz C, Erben P, Ritter M, Bloor A, Metzgeroth G, Telford N, Haferlach C, Haferlach T, Gesk S, Score J, Hofmann

WK, Hochhaus A, Cross NC, Reiter A. Response of ETV6-FLT3-positive myeloid/lymphoid neoplasm with eosinophilia to inhibitors of FMS-like tyrosine kinase 3. Blood. 2011 Aug 25;118(8):2239-42

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