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Leukaemia Section
Mini Review

t(10;12)(q24;p13)

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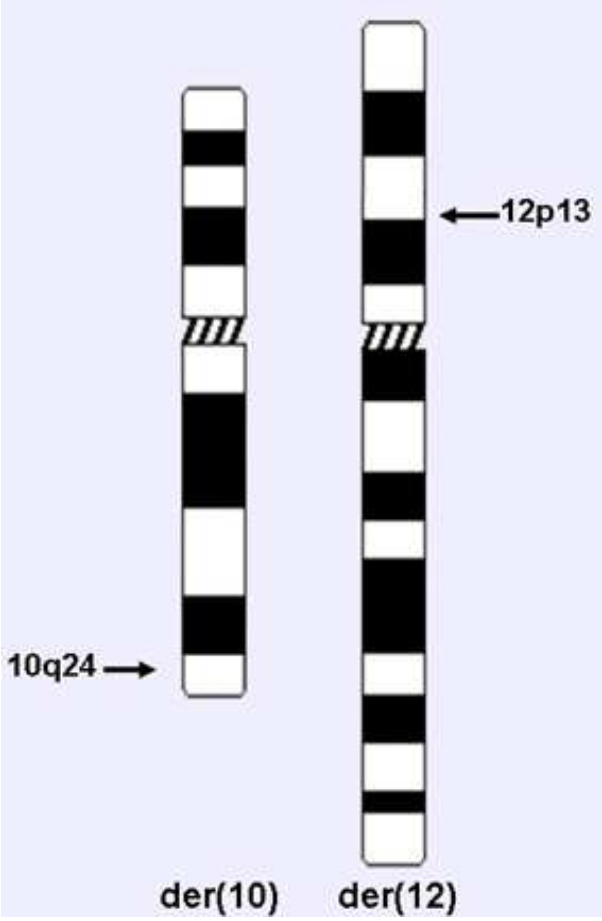
Identity



Scheme of t(10;12)(q24;p13)

Clinics and pathology

Disease

Myeloid disorders:

Myelodysplastic syndrome (MDS) type refractory anemia (RA) (Wlodarska et al., 1995) and refractory anemia with excess blasts (RAEB) (Struski et al., 2008).

Philadelphia chromosome positive chronic myeloid leukemia (CML) in transformation (Aguiar et al., 1997).

Etiology

Only 3 cases so far; 77-year old male (MDS-RA) and 71-year old female (MDS-RAEB). No data available on a case of CML.

Prognosis

Unknown so far.

Cytogenetics

Cytogenetics molecular

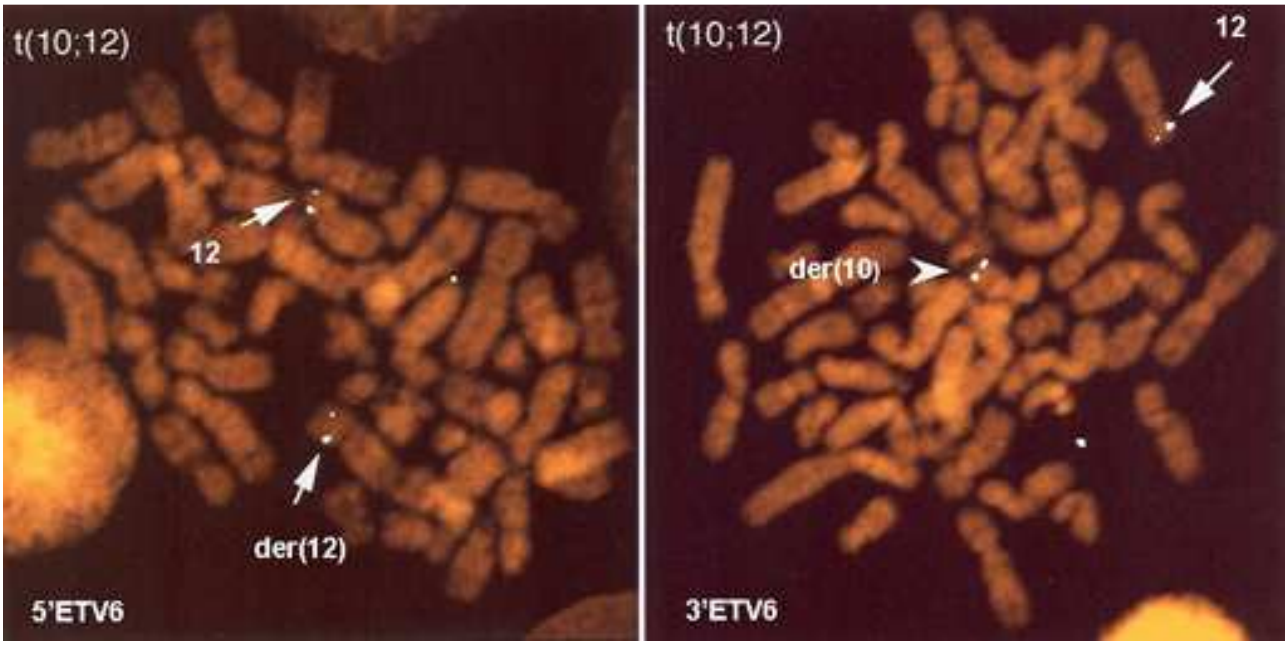
FISH demonstrated ETV6 involvement in both MDS cases. In a case of CML, the 12p13 breakpoint was mapped between ETV6 (11.9 Mb) and GDID4 (15 Mb). In addition, FISH detected a cryptic deletion of CDKN1B (12.7 Mb) associated with this translocation.

Additional anomalies

The translocation was found as a sole aberration in a case of MDS-RA, in a subclone with del(5)(q13q34) in a case of MDS-RAEB, and was accompanying t(9;22)(q34;q11) in a case of CML.

Variants

The ETV6-involving t(10;12)(q24;p13) was recognized as the first variant of t(5;12)(q33;p13) targeting ETV6 and PDGFRB (Wlodarska et al., 1995) (Golub et al., 1994). So far, at least 24 ETV6-associated fusion transcripts have been identified in human malignancies.



FISH with cosmids specific for the 5' end (c179A6) and the 3' end (c148B6) of ETV6 in a case of MDS-RA (Wlodarska et al., 1995).

Genes involved and proteins

ETV6

Location
12p13.2

DNA/RNA
ETV6 encodes an ets (E-26 transforming specific) family transcription factor. Three transcripts have been described: ETV6-202 (8 exons; length 5.974 bps; 452 amino acids), ETV6-203 (10 exons; length 5.697 bps; 451 amino acids) and ETV6-201 (5 exons; length 1836 bps; 61 amino acids). Transcription is from telomere to centromere.

Protein
Two functional domains have been indentified: a N-terminal Helix-Loop-Helix domain (or pointed (PNT) or Sterile Alpha Motif (SAM) domain) responsible for hetero- and homodimerization with itself and possibly other proteins, and a C-terminal ETS domain responsible for a specific DNA binding. HLH domain is encoded by exons 3 and 4, and ETS domain by exons 6-8. As a transcription regulator, ETV6 is localized in the nucleus.
Experimental data suggest that ETV6 is required for hematopoiesis and maintenance of the developing vascular network.

GOT1

Location
10q24

DNA/RNA
9 exons; transcript of 10942 bps. Transcription is from telomere to centromere.

Protein
GOT1 encodes for a cytosolic form of an ubiquitous pyridoxal phosphate-dependent enzyme. The enzyme plays an important role in amino acid metabolism and in the urea and tricarboxylic acid cycles. The GOT1 protein is 413-amino acid long and its predicted molecular weight is 46 kDA.

Result of the chromosomal anomaly

Hybrid gene

Note
Molecular consequences of the seemingly looking t(10;12)(q24;p13) found in MDS and CML seem to be different.

Description
Both MDS cases showed the ETV6-GOT1 transcript formed by an in frame fusion between the first two exons of ETV6 and exon 2 to exon 9 of GOT1 (MDS-RA), or by fusion of exon 3 of ETV6 with exon 2 of GOT1 (MDS-RAEB). In both cases additional not-in frame fusions involving ETV6 and sequences telomeric to GOT1 have been identified.
The t(10;12) found in a case of CML in transformation does not involve ETV6; the 12p13 breakpoint was mapped between ETV6 and GDID4. Whether this translocation results in an in frame fusion or is a bystander event associated with the deletion of CDKN1B detected in this case is unknown.

Fusion protein

Description
The molecular consequences of the ETV6-GOT1

fusion remain unclear. It has been postulated that the fusion protein, only lacking a short N-terminal part of GOT1, can still form heterodimers with wild type GOT1, thereby acting as a dominant negative form, resulting in a reduction of GOT1 enzymatic activity in dysplastic cells. In addition, the translocation could also deregulate the expression of genes located upstream of GOT1 (e.g. c10orf139, found to be overexpressed in the MDS-RA case) or leads to inactivation of ETV6.

References

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