**t(6;12)(q22;p13) ETV6/FRK**

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### Abstract

Review on t(6;12)(q21;p13), with data on the genes involved

**Keywords**

chromosome 6; chromosome 12; acute lymphoblastic leukemia; acute myeloid leukemia; ETV6; FRK

### Clinics and pathology

#### Disease

Translocation t(6;12)(q21;p13) is a rare abnormality, it occurs in both myeloid and lymphoid disorders including AML, ALL, and NHL.

**Acute lymphoblastic leukemia** (ALL) was diagnosed in 6 pediatric patients, 4 of them were with early pre-B ALL (Raimondi et al., 1997; Hayashi et al., 1990), one patient with T-ALL (Kaneko et al., 1989).

**Acute myeloid leukemia** (AML): there were 2 adult patients (Hosoya et al., 2005; Campbell et al., 1994).

**Small lymphocytic lymphoma** was diagnosed in 1 patient (Bloomfield et al., 1983).

#### Epidemiology

The t(6;12)(q21;p13) is a rare reciprocal translocation. Male predominance (Male : Female 3.5 : 1).

### Table 1. Reported cases with t(6;12)(q21;p13).

<table>
<thead>
<tr>
<th>#</th>
<th>Age, gender</th>
<th>Disease:sp;</th>
<th>Karyotype</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7, M</td>
<td>Early pre-B ALL</td>
<td>48,XY,t(6;12)(q21;p13),+16,+add(19)(p13)</td>
<td>Raimondi et al, 1997</td>
</tr>
<tr>
<td>2</td>
<td>5,5, M</td>
<td>Early pre-B ALL</td>
<td>46,XY,inv(12)(p13q22),add(21)(q22)/46,XY,t(6;12)(q21;p13)/46,XY,t(6;12),inv(12)</td>
<td>Raimondi et al, 1997</td>
</tr>
<tr>
<td>3</td>
<td>?, M</td>
<td>ALL</td>
<td>46,XY,t(6;12)(q21;p13)/46,XY</td>
<td>Katz et al, 1991</td>
</tr>
<tr>
<td>4</td>
<td>?, M</td>
<td>Early pre-B ALL</td>
<td>48,XY,+16,+der(19)(19;19p13;7)/46,XY,t(6;12)(q21;p13)/46,XY,+16,+der(19)(d e1(12)(p13);6)(12)</td>
<td>Hayashi et al., 1990</td>
</tr>
<tr>
<td>5</td>
<td>?, M</td>
<td>Early pre-B ALL</td>
<td>46,XY,inv(12)(p13q22)/21,-21,der(21)(q22);q22)/46,XY,t(6;12)(q21;p13)/46,XY,t(6;12),inv(12)</td>
<td>Hayashi et al., 1990</td>
</tr>
<tr>
<td>6</td>
<td>10, F</td>
<td>T-cell ALL</td>
<td>46XX,t(6;12)(q21;p13),t(7;14)(p15q32)</td>
<td>Kaneko et al., 1989</td>
</tr>
<tr>
<td>7</td>
<td>69, M</td>
<td>Small Lymphocytic Lymphoma</td>
<td>46,XY,t(6;12)(q21;p13),+der(7)(7q34;?)+der(17)(17;17p13;?)+20</td>
<td>Bloomfield 1983</td>
</tr>
<tr>
<td>8</td>
<td>69, F</td>
<td>AML</td>
<td>46XX,t(6;12)(q21;p13)</td>
<td>Hosoya et al., 2005</td>
</tr>
<tr>
<td>9</td>
<td>55, M</td>
<td>AML with maturation (FAB type M2)</td>
<td>54,XY,t(6;12)(q21;p13),+8,+9,+10,+11,+13,+14,add(17)(11p11),+20,+del(20)(q11),+21</td>
<td>Campbell et al., 1994</td>
</tr>
</tbody>
</table>
### Prognosis
Survival in ALL and AML patients was 40, 106+ and 5 months respectively (Raimondi et al, 1997; Hosoya et al, 2005).

### Cytogenetics

#### Additional anomalies
Sole abnormality in 2 patients (1 ALL, 1 AML). Additional chromosome anomalies were observed in 6/8 patients.
In early pre B-ALL t(6;12)(q21;p13) was associated in combination with extra chromosome 16 in 2 patients, and a complex karyotype in 2 cases (Hayashi et al., 1990; Raimondi et al., 1997). In small lymphocytic lymphoma, t(6;12)(q21;p13) is part of a complex karyotype.

### Genes involved and proteins

#### ETV6 (ets variant 6)
**Location** 12p13.2
**Protein**
ETV6 encodes an ETS family transcription factor. ETV6 protein contains two functional domains: a N-terminal pointed (PNT) domain that is involved in protein-protein interactions with other proteins, and a C-terminal DNA-binding domain.
Gene knockout studies suggest that it is required for hematopoiesis and maintenance of the developing vascular network.
ETV6 is known to be involved in a large number of chromosomal abnormalities associated with leukemia and inborn fibrosarcoma.

#### FRK (Fyn-related Src family tyrosine kinase)
**Location** 6q22.1
**Protein**
FRK belongs to a family of SRC kinases. SRC is the prototype for a family of genes that encode non-receptor tyrosine kinases implicated in a variety of cellular processes. The wild type FRK is expressed primarily in epithelial tissues, but also weakly in the various hematopoietic cell lines. However, its functions or downstream signaling pathways remain largely unknown, especially in hematopoietic systems. The only known candidate endogenous downstream component of FRK is the SH2-domain adaptor protein SHB (Hosoya et al., 2005).

### Result of the chromosomal anomaly

#### Hybrid gene
In the resultant ETV6/FRK fusion protein, the entire PNT oligomerization domain of ETV6 and the kinase domain of FRK are fused in frame.

#### Fusion protein

**Oncogenesis**
It has been shown that ETV6/FRK is an oncoprotein with dual functions: deregulated tyrosine kinase activity and a dominant-negative modulation of transcriptional repression by ETV6. Because wild-type ETV6 appears to have tumor-suppressive activity, its suppression by ETV6/FRK also could contribute to oncogenesis (Hosoya et al., 2005).

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**Figure 1.** Schematic representation of wild-type ETV6, FRK, and the fusion transcript ETV6/FRK. The breakpoints are indicated by vertical arrows.
References


Campbell LJ, Garson OM. The prognostic significance of deletion of the long arm of chromosome 20 in myeloid disorders. Leukemia. 1994 Jan;8(1):67-71


This article should be referenced as such: