

# Leukaemia Section

## Short Communication

### **t(6;14)(p25;q32) IRF4/IGH / t(2;6)(p12;p25) IRF4/IGK / t(6;22)(p25;q11) IRF4/IGL**

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## Identity

### Note

The t(6;14) translocation juxtaposing the immunoglobulin heavy chain gene to the IRF4 gene have been shown to activate the transcription factor MUM1/IRF4 in multiple myeloma and in a subtype of mature B-cell lymphomas (Iida et al., 1997; Salaverria et al., 2011).

The translocation leads to the overexpression of the MUM1/IRF4 gene.

In multiple myeloma, IRF4 is similarly juxtaposed by an illegitimate IG switch recombination to the IG loci (Iida et al., 1997).

Moreover, in multiple myeloma, expression of IRF4 is not only driving those cases with IG/IRF4-fusion but is also essential for survival in cases lacking this translocation (Shaffer et al., 2008).

Specifically IGH/IRF4 and its variants fusions are associated with a subgroup of GC B-cell lymphomas composing follicular lymphoma grade 3 or centroblastic DLBCL characterized by coexpression of MUM1 and BCL6 in the absence of PRDM1/BLIMP1, a specific gene expression profile, and a disease onset predominantly in childhood or young adulthood (Salaverria et al., 2011).

## Clinics and pathology

### Disease

Multiple myeloma (MM)

### Phenotype/cell stem origin

Plasma Cell. MUM1<sup>+</sup>/BCL6<sup>+</sup>/BLIMP1<sup>+</sup>.

### Epidemiology

Rare translocation, <1% (Tamura et al., 2000). Not one of the five recurrent IGH translocations in MM (Swerdlow et al., 2008).

### Clinics

Unknown.

### Prognosis

As a result, the MUM1/IRF4 gene is overexpressed, an event that contributes to tumorigenesis.

The clinical significance of this alteration in MM remains unknown.

### Disease

B-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma

### Phenotype/cell stem origin

Germinal Center derived. MUM1<sup>+</sup>/BCL6<sup>+</sup>/BLIMP1<sup>-</sup>.

### Epidemiology

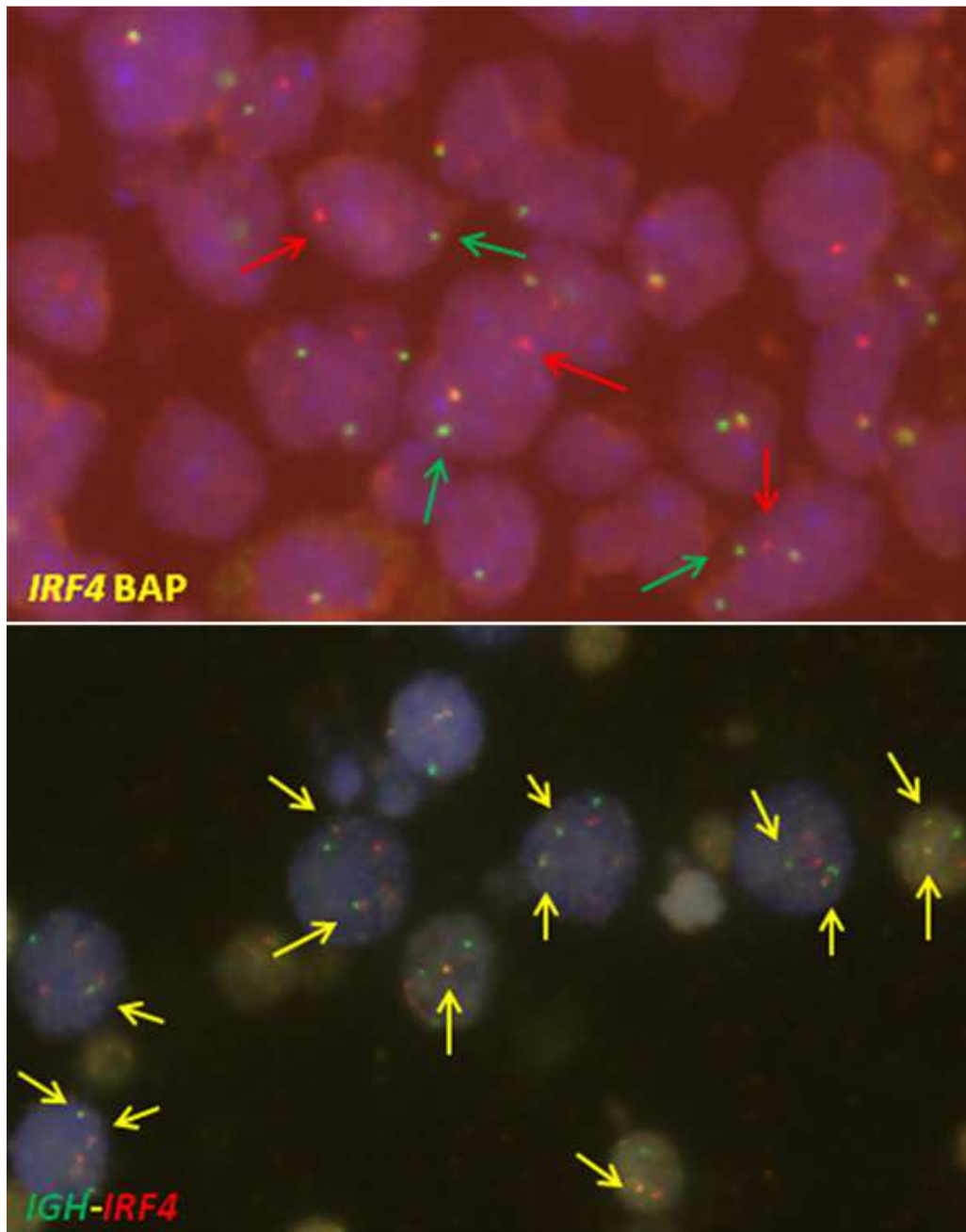
Rare translocation. Present in 15% and 2% of the pediatric and adult GCB derived B-cell lymphomas respectively (Salaverria et al., 2011).

### Clinics

Clinical presentation is significantly skewed toward the involvement of the head and neck region, including Waldeyer ring and limited disease stages (Salaverria et al., 2011).

### Prognosis

IG/IRF4-positive cases are associated with a significantly better prognosis, although this effect is



Fluorescence in situ hybridization (FISH) analyses for the detection of IRF4 breaks in, the signal constellation shows IRF4 breaks and IGH-IRF4 fusion in two cases of B-cell lymphoma respectively.

predominantly associated with the low age of the positive cases (Salaverria et al., 2011; Klapper et al., 2012).

## Genetics

### Note

In MM, three cell lines have showed fusions between these two loci, which resulted in the juxtaposition of the MUM1 to the IgH 3' alpha-enhancer region by virtue of t(6;14) or insertion of the IgH sequences into the vicinity of the MUM1 gene and in the concomitant overexpression of the MUM1 mRNA (Yoshida et al., 1999).

In germinal center derived lymphomas, long-distance inverse PCR for cloning the IGH partner have been used. S $\mu$ -long-distance inverse PCR has detected a switch  $\mu$ -associated translocation t(6;14)(p25;q32) in two cases. Both translocations disrupted the coding region of EXOC2. Immediately telomeric of EXOC2 maps the IRF4 gene, which through the translocation is juxtaposed to the IGH locus on the der(14)t(6;14) in the same transcriptional direction (Salaverria et al., 2011). The breakpoints might be located on either side of IRF4 and can affect the DUSP22 gene, immediately telomeric and the EXOC2 gene centromeric to IRF4.

In this sense, a recent sequencing study has described in a young DLBCL patient carrying a fusion between 6p25 and 14q32, juxtaposing IGH with the DUSP22 gene (Morin et al., 2011).

## Cytogenetics

### **Cytogenetics morphological**

t(6;14)(p25;q32) is cytogenetically cryptic, not detectable by means of conventional cytogenetic analysis (Yoshida et al., 1999).

### **Cytogenetics molecular**

FISH constellation have demonstrated juxtaposition of IGH and IRF4.

### **Additional anomalies**

In germinal center derived lymphomas, the IG/IRF4-positive lymphomas had fewer chromosomal imbalances suggesting that the IRF4 translocation is an early event in lymphomagenesis. In MM, the secondary copy number changes of the positive cases are unknown.

### **Variants**

Light chain variants t(2;6)(p12;p25), t(6;22)(p25;q11). IRF4 breakpoints with unknown translocation partner.

## Genes involved and proteins

### **IRF4 (interferon regulatory factor 4)**

#### **Location**

6p25

#### **DNA/RNA**

9 exons.

#### **Protein**

Lymphocyte specific; The transcription factor MUM1/IRF4 is required during an immune response for lymphocyte activation and the generation of immunoglobulin-secreting plasma cell.

### **IGH (immunoglobulin heavy locus)**

#### **Location**

14q32

#### **DNA/RNA**

IgH is composed of IGHV genes, IGHD segments, IGHJ segments, and IGHC genes.

#### **Protein**

IgH encodes the immunoglobulin heavy chains.

## Result of the chromosomal anomaly

### **Hybrid gene**

#### **Description**

IRF4 translocated on chromosome 14.

## **Fusion protein**

### **Description**

No fusion protein; the immunoglobulin gene enhancer stimulates the expression of IRF4.

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