

**t(4;14)(p16;q32)** (updated: old version not available)

**Clinics and Pathology**

**Disease** found in [plasma cell leukaemia](#), [multiple myeloma](#), plasmacytoma and monoclonal gammopathy of unknown significance (MGUS)

**Phenotype / cell stem origin** malignant plasma cells have the phenotype of mature terminally differentiated B-cells; their origin may be a pluripotent stem cell

**Epidemiology** poorly described before FISH, quite karyotypically undetectable: found initially in cell lines, it represents the second most frequent IgH associated rearrangement, after t(11;14); detected by interphase FISH or RT-PCR in 25% MM cell lines, 15-20% primary MM and 0-10% MGUS lines; might be frequent but karyotypically undetected

**Clinics** found in MM cases with unfavorable prognosis, even in patients treated with high dose chemotherapy IMAGE

**Cytogenetics**

**Cytogenetics** may be undetectable (telomere-telomere translocation)

**Morphological**

**Cytogenetics** therefore molecular probes are indicated, and FISH is relevant.

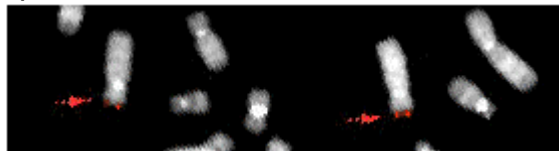
**Molecular**

**Additional anomalies** hypodiploid karyotype and -13 / 13q- in major part of cases

**Genes involved and Proteins**

**Gene Name** [FGFR3](#)

**Location** 4p16.3



[c-FGFR3](#) (4p16.3) in normal cells: PAC 884J17 - Courtesy Mariano Rocchi, [Resources for Molecular Cytogenetics](#). Laboratories willing to validate the probes are welcome: contact [M Rocchi](#)

**Protein** Member of the tyrosine-kinase FGF receptor family, contains an extracellular domain with Ig-like loops, a transmembrane domain, and intracellular tyrosine kinase domains; localisation: plasma membrane; tyrosine kinase receptor; role in signal transduction, activates multiple signaling pathways regulating cell proliferation and differentiation; constitutional point mutations resulting in ligand-independent activation, are responsible of familial dominant achondroplasia / thanatophoric dwarfism.

**Gene Name** [IgH MMSET \(multiple myeloma SET domain\), also known as WHSC1 \(Wolf-](#)

### [Hirschorn syndrome candidate 1\)](#)

Location	14q32 4p16.3
Dna / Rna	90 kb, 25 exons, 5' - 3' centromeric orientation - complex alternative splicing
Protein	136 KDa, 4 domains: PWWP domain (proline-tryptophan-tryptophan-proline motif), HMG box (high mobility group), PHD-type (plant-homeodomain) zinc finger domain and SET (suppressor of variegation enhancer of zeste and Trithorax) domain. One full length 1365 aa isoenzyme and 4 possible truncated variants. Transcription factor, ubiquitously expressed but preferentially in growing embryonic tissues. Chromatin remodelling agent, regulates histones methylation. Constitutional deletion of one copy is responsible for Wolf-Hirschhorn syndrom by haplo-insufficiency.

### Result of the chromosomal anomaly

#### Hybrid gene

Description	4p16.3 breakpoint in a 110 kb region between MMSET (centromeric) within the 5' introns, and FGFR3 (telomeric) 14q32 breakpoint in the IgH switch region involving JH + constant region Two fusions generated, FGFR3 brought under the influence of the Ig gene enhancer Ea on der(14); MMSET under the influence of enhancer Eμ on der(4). Both FGFR3 and MMSET genes are deregulated by the translocation and a IgH-MMSET fusion transcript, detectable by RT-PCR, is generated.
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#### Fusion Protein

Description	no IgH-FGFR3 fusion protein, but promoter exchange between both partner genes; however, somatic mutations similar to what has been found in thanatophoric dwarfism have been identified in some cases; they may also contribute to abnormal FGFR3 activation. According to the variable breakpoint inside MMSET gene, the translocation may generate either a full length MMSET protein or a NH2-terminal truncated one.
Oncogenesis	overexpression and activation of FGFR 3 provides an oncogenic signal enhancing cell proliferation and survival. The functional consequences of MMSET deregulation are not completely investigated. All t(4;14) positive cases express MMSET whereas 30% lack FGFR3 expression, sometimes correlated with loss of der(14), which tends to demonstrate that MMSET dysregulation should be the crucial oncogenic event.

### External links

Other database	<a href="#">t(4;14)(p16;q32)</a>	<a href="#">Mitelman database (CGAP - NCBI)</a>
Other	<a href="#">t(4;14)(p16;q32)</a>	<a href="#">CancerChromosomes (NCBI)</a>

database

## To be noted

Additional cases are needed to delineate the epidemiology of this rare entity:  
**you are welcome to submit a paper to our new [Case Report](#) section.**

## Bibliography

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**Contributor(s)**

**Written** 03-1998 Jean-Loup Huret and Jacky Bonaventure

**Updated** 05-2005 Frank Viguié

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