

# Leukaemia Section

## Review

# 8p11 myeloproliferative syndrome (EMS, eight p11 myeloproliferative syndrome)

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## Identity

### Alias

Stem cell leukemia-lymphoma syndrome (SCLL); 8p11 stem cell syndrome; 8p11 stem cell leukemia/lymphoma syndrome; Myeloid and lymphoid neoplasms FGFR1 abnormalities (WHO 2008 proposal)

### Note

Although "8p11 myeloproliferative syndrome" (EMS) (Macdonald et al., 1995) is the most frequent name for this disease in the literature, it must be designated as "myeloid and lymphoid neoplasm with FGFR1 abnormalities" under the current 2008 World Health Organization classification (Tefferi and Vardiman, 2008; Tefferi et al., 2009). This disease has been referred to as "stem cell leukemia/lymphoma" (SCLL) (Inhorn et al., 1995) which remark the coexistence of lymphoma, myeloid malignancy and lymphoblastic leukemia.

## Clinics and pathology

### Note

This disease is related to fusion genes between FGFR1, located in 8p11, and several partner genes. However there are some other aberrations affecting this chromosomal band and 8p12 in other neoplasms. Some acute myeloid leukemia (AML) cases have been described related to translocations affecting MYST3 (also known as MOZ) (Borrow et al., 1996; Carapeti et al., 1998; Chaffanet et al., 2000; Murati et al., 2007; Esteyries et al., 2008; Gervais et al., 2008) and WHSC1L1 (also known as NSD3) (Rosati et al., 2002; Romana et al., 2006; Taketani et al., 2009), both of them in 8p11. In addition, aberrations in 8p11-p12 are also frequent events in breast cancer, but the loci

responsible are not well known (Yang et al., 2004; Garcia et al., 2005; Gelsi-Boyer et al., 2005; Pole et al., 2006; Yang et al., 2006; Yang et al., 2010).

### Disease

Clinical entity defined by the disruption of the FGFR1 gene located at 8p11 with generation of a fusion gene between the 3' part of FGFR1 and the 5' part of the partner gene that also provides its promoter. The partner gene is always expressed in the haematopoietic system and codes for a protein with oligomerization domains. As a result of oligomerization, chimeric proteins show constitutive and ligand-independent activation of FGFR1 kinase activity.

The 8p11 myeloproliferative syndrome (EMS) is a myeloproliferative disease with multilineage involvement characterized by chronic myelomonocytic leukemia (CMML)-like myeloid hyperplasia, marked peripheral blood eosinophilia and associated with a high incidence of non-Hodgkin's lymphoma, usually of the T-cell lymphoblastic subtype. Occasional cases also show a B-cell lymphoproliferative disorder (Macdonald et al., 2002).

EMS cases were already described in the 1970s and 1980s, but cytogenetic and molecular analyses were not available (Manthorpe et al., 1977; Kjeldsberg et al., 1979; Catovsky et al., 1980; Posner et al., 1982). In 1992, 3 cases of T-cell lymphoblastic lymphoma associated with eosinophilia that subsequently developed acute myeloid leukemia or myelodysplastic/myeloproliferative neoplasms were reported (Abruzzo et al., 1992). One of them showed a t(8;13) by conventional cytogenetics. Later it was shown that one of the breakpoints involved one 8p11 locus (Xiao et al., 1998). In the same year, Rao et al. reported a patient with t(8;13)(p11;q12) who presented with leukocytosis, monocytosis, myeloid hyperplasia of

bone marrow, and generalized lymphadenopathy due to T-cell lymphoblastic lymphoma (Rao et al., 1998). The term 8p11 myeloproliferative syndrome was suggested in 1995 by Macdonald et al. (Aguilar et al., 1995; Macdonald et al., 1995) and confirmed as clinical entity (SCLL) by Inhorn et al. (Inhorn et al., 1995).

### **Phenotype/cell stem origin**

The presence of the cytogenetic aberration in 8p11 both in myeloid and lymphoid cells, suggest a bilineage differentiation from a pluripotent and common stem cell (Macdonald et al., 2002).

### **Etiology**

The FGFR1 fusion proteins that result from chromosomal translocations affecting 8p11 have constitutive and ligand-independent FGFR1 enzymatic activity. FGFR1 is a receptor tyrosine kinase that dimerizes upon ligand binding, activating multiple signalling pathways like Ras/MAPK, PI3K, PLCgamma and STAT. These pathways could be abnormally activated as consequence of FGFR1 aberration (Macdonald et al., 2002) resulting in cell transformation. In fact, expression of ZMYM2-FGFR1 and BCR-FGFR1 fusions in immunodeficient mice are capable of initiating an EMS-like disease (Agerstam et al., 2010). Different fusion proteins could activate these pathways in a different way and could explain the phenotypic variability of the disease (Roumiantsev et al., 2004; Cross and Reiter, 2008; Jackson et al., 2010).

### **Epidemiology**

This is a very rare disease with less than 100 patients reported around the world and it can be found at any age. It has been reported at ages ranging from 3 to 84 years (median: 44 years). There is a slightly male-to-female predominance (Macdonald et al., 2002; Jackson et al., 2010).

### **Clinics**

Around 20-25% of patients show systemic and unspecific symptoms like fatigue, night sweats, weight loss and fever and around 20% are asymptomatic (and the disease is detected in routine analyses). Near two thirds of patients show lymphadenopathy, generalized or localized. Hepato- and/or splenomegaly are also frequent events in these patients. One of the distinctive features of this disease is the high frequency of lymphoblastic lymphoma, uncommon in other myeloproliferative neoplasms (Macdonald et al., 2002; Jackson et al., 2010).

### **Cytology**

It seems that neoplastic cells present in lymph nodes are predominantly small or medium lymphoblasts with a small cytoplasm (Jackson et al., 2010).

### **Pathology**

The blood counts reported are variable. More than 90% of patients have leukocytosis and less than 10% have

leukopenia but some cases have been reported with normal leukocyte counts. Eosinophilia is frequent, but monocytosis appears only in one third of patients. Basophils are increased only in cases with the t(8;22)(p11;q11). Blasts have been detected in half of the patients and some cases show blast counts typical of an acute leukemia. These blasts are mainly of a myeloid or myeloid and lymphoid (bilineal) lineage although some of them are also of an immature lymphoid lineage.

Most of the patients show a hypercellular bone marrow that leads to a diagnosis of myeloid hyperplasia or a myeloproliferative neoplasm. But in some cases, the dysplastic features lead to a diagnosis of myelodysplastic syndrome or a myelodysplastic syndrome/myeloproliferative neoplasm.

Most of the cases with lymph node biopsies reported had T-lymphoblastic lymphoma and the rest had myeloid sarcoma. In some cases evidence of bilineal T-cell/myeloid or B- and T- cell lymphoblastic lymphoma has been reported. For a review see Jackson et al., 2010.

### **Treatment**

This is a very aggressive disease with a high rate of progression to an AML resistant to conventional chemotherapy with a median survival time of less than 12 months (Macdonald et al., 2002; Cross and Reiter, 2008; Jackson, 2010).

There are very few cases (Martinez-Climent et al., 1998; Zhou et al., 2010) responding to interferon alpha, this treatment could be useful at early stages. However, to date, only stem cell transplant remains effective to eradicate or suppress the malignant clone (Macdonald et al., 2002; Jackson et al., 2010). Median survival time for patients who received transplant after transformation to AML is 24 months (range 6-46 months) but median survival time is 12 months for the patients who did not received transplant (range 0-60 months) (Jackson et al., 2010). Currently there are no specific inhibitors for clinical use effective in this disease. Patients with FGFR1 fusions do not respond to drugs developed for other tyrosine kinases like imatinib, although several FGFR1 inhibitors have been tested, some of them with promising effects (Zhang et al., 2010; Zhou et al., 2010; Bhide et al., 2010; Risuleo et al., 2009; Ma et al., 2008; Cai et al., 2008; Chase et al., 2007; Kammassud et al., 2007; Klenke et al., 2007; Chen et al., 2004; Aviezier et al., 2000).

### **Evolution**

This disease has a chronic phase characterized by myeloid hyperplasia and overproduction of myeloid cells that can differentiate, but without treatment the disease progresses rapidly (1 to 2 years after diagnosis) to an acute myeloid leukemia (AML) or sometimes to a B-lineage ALL (Macdonald et al., 1995; Inhorn et al., 1995; Macdonald et al., 2002; Jackson et al., 2010).

Gain of an additional copy of chromosome 21 is a non-random cytogenetic event apparently associated with progression of this disease (Agerstam et al., 2007; Goradia et al., 2008) but its role remains unclear (Jackson et al., 2010). This abnormality is reported in only 5 of 47 (10.6%) karyotypes at the time of diagnosis but in 10 of 13 (76.9%) karyotypes reported in follow-up. These karyotypes were mostly derived during clinical deterioration. In addition, some findings at the time of transformation from EMS to acute leukemia include the addition of various marker chromosomes, as well as trisomy of chromosomes 8, 9, 12 or 19 and deletions of chromosome 7 or either the 7p or 7q arms, and derivative chromosome 9 (Jackson et al., 2010).

### Prognosis

As mentioned before, this is a devastating disease, which transforms to acute leukemia in a few months if left untreated, and in which the malignant clone cannot be eradicated by conventional chemotherapy. So at this moment, without specific FGFR1 inhibitors for clinical use, the stem cell transplant remains as the only possibility to a long-term survival (Macdonald et al., 1995; Inhorn et al., 1995; Macdonald et al., 2002; Jackson et al., 2010).

## Genetics

### Note

This disease is defined by the fusion of FGFR1 (8p11) with other partner genes, as consequence of a cytogenetic aberration, mainly chromosomal translocations. FGFR1 codes for a receptor tyrosine kinase. The gene fusion maintains the 3' terminal part of the FGFR1 gene (from exon 9) joined to the 5' terminal part of the partner gene. Partner genes are widely expressed and fusion genes have also this expression pattern. The chimeric gene codes for a protein which retains the TK domain from FGFR1 and oligomerization domains provided by the partner gene. This protein has a constitutive and ligand-independent activity and activates multiple signal transduction pathways.

## Cytogenetics

### Variants

#### **t(8;13)(p11;q12) ZMYM2-FGFR1**

This is the first translocation described (Xiao et al., 1998; Reiter et al., 1998; Smedley et al., 1998; Popovici et al., 1998) and the most common one. In fact, it has been described in 33 of the 65 cases described until now (Jackson et al., 2010).

This translocation generates a fusion gene ZMYM2-FGFR1.

Patients with this translocation develop lymphadenopathy and T-cell lymphoblastic lymphoma

(Macdonald et al., 2002; Cross and Reiter, 2008; Jackson et al., 2010).

#### **t(6;8)(q27;p11) FGFR1OP-FGFR1**

This translocation was first described by Popovici et al. (1999) and fuses FGFR1OP (previously known as FOP-FGFR1 oncogene partner-) with FGFR1.

As other FGFR1 fusion variants, the chimeric FGFR1OP-FGFR1 protein retains the N-terminus leucine-rich region of FGFR1OP (an oligomerization domain) fused to the catalytic domain of FGFR1 driving the abnormal oligomerization of the chimeric protein and a constitutive and ligand-independent activation.

This translocation has been reported in 8 cases until date (Vizmanos et al., 2004). Eosinophilia is frequent in these patients. Four of these patients had features at presentation and/or a clinical course typical of EMS, but three showed polycythemia vera (PV) and another one B-ALL.

#### **t(8;9)(p12;q33) CEP110-FGFR1**

This translocation was described in 1983 but molecularly characterized by Guasch et al. in 2000 (Guasch et al., 2000).

This translocation has been reported in more than ten cases until date (Mozziconazzi et al., 2008; Jackson et al., 2010) and the MPD caused by this aberration transforms rapidly and always in myelomonocytic leukemia, with a possible B- or T-lymphoid involvement. In addition, tonsillar involvement and monocytosis also correlates with this variant (Mozziconazzi et al., 2008; Jackson et al., 2010). Recently a complete haematological and molecular remission has been reported after two years in a patient with this translocation treated early with interferon alpha (Zhou et al., 2010).

#### **t(8;22)(p11;q11) BCR-FGFR1**

This translocation was reported simultaneously by two groups in 2001 (Fioretos et al., 2001; Demiroglu et al., 2001) and fuses BCR with FGFR1.

As in the case of the other FGFR1 fusions, BCR is also widely expressed and BCR-FGFR1 retains oligomerization domains from BCR and the catalytic domain from FGFR1, leading to constitutive and ligand-independent activity of the chimeric protein. However it seems that BCR not only drives this oligomerization but could also play some role in triggering the downstream signalling pathways. Patients with BCR-FGFR1 fusions have a slightly different clinical phenotype from other FGFR1 fusion variants. In fact, these patients have a clinical and morphological picture similar to typical BCR-ABL positive chronic myeloid leukemia (Roumiantsev et al., 2004; Cross and Reiter, 2008; Baldazzi et al., 2010; Jackson et al., 2010).

#### **t(8;11)(p11;p15) NUP98-FGFR1**

This translocation was described by Sohal et al. in 2001, in a patient with AML with additional cytogenetic aberrations (patient UPN6,

47,XY,t(8;11)(p11;p15),+8,-17,+i(17q)) (Sohal et al., 2001). Only interphase cells were available to perform FISH analysis, and the results obtained indicated a breakpoint within or in the vicinity of NUP98 but definite molecular characterization could not be done. Other patient with AML and the same translocation had been reported previously (Larson et al., 1983), indicating that this was a recurrent abnormality. However no new cases have been described since these reports so NUP98-FGFR1 fusion has not been confirmed definitely. NUP98 has a small coiled-coil region that could drive the constitutive activation of the chimeric NUP98-FGFR1 protein but it is possible that disruption of NUP98 was also involved in the oncogenic process.

#### **t(8;19)(p11;q13) HERVK-FGFR1**

This aberration was firstly described in 2000, associated with loss of the Y chromosome in a man with an AML M0, probably secondary to a myeloproliferative disorder, who died 15 months after diagnosis (Mugneret et al., 2000). Later, the same group identified the chromosome 19 partner showing that a long terminal repeat of human endogenous retrovirus gene (HERV-K) was fused in frame with FGFR1 (Guasch et al., 2003). This fusion has been described only in this case.

#### **ins(12;8)(p11;p11p22) FGFR1OP2-FGFR1**

This FGFR1 fusion is not caused by a chromosomal translocation but an inversion. Ins(12;8)(p11;p11p22) targeting FGFR1 was first described by Sohal et al. (2001) in a 75-years old patient diagnosed with a T-cell lymphoblastic lymphoma and marked lymph node infiltration with atypical eosinophils. Whole blood count was normal except for very mild eosinophilia and the bone marrow also showed some atypical eosinophils. After complete remission, this patient relapsed and transformed to an AML with the same chromosomal aberration and died. Later this aberration was molecularly characterized by the same group (Grand et al., 2004) as a fusion between FGFR1OP2 (from FGFR1 oncogene partner 2) located at 12p11.23 and FGFR1. Fusion structure was identical to other FGFR1 variants.

This fusion has been reported only in one case (Sohal et al., 2001; Grand et al., 2004) but it has been also found in the cell line KG-1 (Gu et al., 2006; DSMZ ACC 14) that can be used to assay in vitro specific FGFR1 inhibitors (Gu et al., 2006; Chase et al., 2007). This cell line was derived from the bone marrow of a 59-year-old man with erythroleukemia transformed to AML at relapse in 1977 (Koeffler and Golde, 1978).

#### **t(7;8)(q34;p11) TRIM24-FGFR1**

This translocation was described and molecularly characterized by Belloni et al. (2005) in a 49-year-old woman with a putative chronic MPD with eosinophilia which transformed to an AML-M4 and died in a few days. As other FGFR1 fusions, this is the only case reported to date.

The consequence of the t(7,8)(q34;p11) is the fusion gene TRIM24-FGFR1.

#### **t(8;17)(p11;q23) MYO18A-FGFR1**

This translocation was described by Walz et al. (2005) in a 74-year-old female with a 2 years history of an unusual myelodysplastic/myeloproliferative disease (MDS/MPD) with thrombocytopenia, markedly reduced size and numbers of megakaryocytes and elevated numbers of monocytes, eosinophils and basophils. Her karyotype showed an additional trisomy 20 and she died after a treatment-resistant disease progression of two years.

This translocation fuses MYO18A, located in 17q11.2 with FGFR1. However, the breakpoint in chromosome 17 was cytogenetically located to 17q23. FISH and molecular analysis showed that this fusion gene was consequence of a complex cytogenetic aberration with an additional inversion in 17q region between 17q11 and 17q23.

#### **t(8;12)(p11;q15) CPSF6-FGFR1**

This translocation targeting FGFR1 was first described by Sohal et al. (2001). Later the same group identified the partner gene as CPSF6 (located at 12q15) (Hidalgo-Curtis et al., 2008) and again, only this case has been described. The patient was a 75-year-old female with lymphadenopathy, splenomegaly, neutrophilia and eosinophilia in peripheral blood and also an increase of eosinophils and eosinophil precursors in the bone marrow. After a rapid clinical deterioration the patient died in 10 weeks.

#### **t(2;8)(q37;p11) LRRFIP1-FGFR1**

In 2009, Soler et al. identified and characterized the t(2;8)(q37;p11) in an 82-year-old man with 10% eosinophils, 2-4% myelocytes and metamyelocytes, and 8% circulating blasts and an hypocellular bone marrow with moderate dysgranulopoiesis and 15% blasts (Soler et al., 2009). Some years before, this patient had displayed pancytopenia and a bone marrow showing a refractory anemia with an excess of blasts (15%). The disease transformed to AML in one year and the patient died. FISH analysis on retrospective samples showed that the t(2;8)(q37;p11) was not present in early stages (pancytopenia) of the disease.

## Genes involved and proteins

### **ZMYM2**

#### **Location**

13q12

#### **Protein**

ZMYM2 (also known as ZNF198, RAMP -rearranged in atypical myeloproliferative disorder-, or FIM - fused in myeloproliferative disorder) codes for a zinc finger protein that may act as a transcription factor involved in ribosomal RNA transcription and also could be part of a BHC histone deacetylase complex. The chimeric

protein retains the proline-rich domain of ZMYM2 (an oligomerization domain) and the tyrosine kinase domain of FGFR1. The abnormal oligomerization of the chimeric protein leads to constitutive and ligand-independent activation. In addition, this abnormal protein is located in the cytoplasm and not in the membrane as native FGFR1.

### **FGFR1OP**

#### **Location**

6q27

#### **Protein**

FGFR1OP, widely expressed, codes for a hydrophilic centrosomal protein that could be a member of a leucine-rich protein family, and it is involved in the anchoring of microtubules (MTS) to subcellular structures. FGFR1OP could play a role in lung cancer growth and progression and has been proposed as a prognostic biomarker for this disease (Mano et al., 2007).

### **CEP110**

#### **Location**

9q33.2

#### **Protein**

CEP110 encodes also a centrosomal protein with several leucine zipper motifs required for the centrosome to function as a microtubule organizing center. CEP110 is also widely expressed and CEP110-FGFR1 retains the leucine zipper motifs of CEP110 at its N-terminus which could mediate the constitutive activation of the FGFR1 catalytic domain at its C-terminus. In addition the CEP110-FGFR1 fusion protein has been found in the cytoplasm, whereas both CEP110 and FGFR1 wild-type proteins are centrosome and plasma membrane-bound proteins respectively (Guasch et al., 2000).

### **BCR**

#### **Location**

22q11.2

#### **Protein**

BCR is, like ETV6, a common fusion partner of several tyrosine kinase genes rearranged in myeloid disorders (BCR-ABL, BCR-JAK2, BCR-PDGFR and BCR-FGFR1 have been described to date). However function of the protein encoded by this gene is not clear and its name comes from breakpoint cluster region.

### **NUP98**

#### **Location**

11p15

### **HERVK**

#### **Location**

7p22.1

#### **Protein**

HERV-K is also ubiquitously expressed. The HERV-Ks are human specific endogenous retrovirus that have been proposed as etiological cofactors in some chronic diseases like cancer because they are mobile elements that could disrupt tumor suppressor and/or DNA repair genes. In this case, it seems that the part of the HERV-K sequence fused showed similarities with a retroviral envelope protein whose dimerization would induce the constitutive activation of the chimeric protein HERVK-FGFR1 (Guasch et al., 2003).

### **FGFR1OP2**

#### **Location**

12p11.23

#### **Protein**

As other FGFR1 partners, FGFR1OP2 is also widely expressed but its function is unknown. It could code for a cytoskeleton molecule (Lin et al., 2010). However, the putative protein coded by this gene has four potential coiled-coil domains and the first two are retained in the chimeric protein, so they could mediate its oligomerization and constitutive activation (Grand et al., 2004).

### **TRIM24**

#### **Location**

7q34

#### **Protein**

TRIM24 (previously known as TIF1) codes for a protein of the tripartite motif (TRIM) family that mediates transcriptional control by interaction with several nuclear receptors and localizes to nuclear bodies. The tripartite motif includes three zinc-binding domains - a RING, a B-box type 1 and a B-box type 2 - and a coiled-coil region that is retained in the chimeric protein so it could promote, as other FGFR1 fusion proteins, its constitutive and ligand-independent activation

### **MYO18A**

#### **Location**

17q11.2

#### **Protein**

MYO18A is a widely expressed gene that codes for a protein of unknown function of the myosin superfamily. It has been recently described that this protein is a novel PAK2 (p21-activated kinase 2) binding partner (Hsu et al., 2010). PAK2 has many biological functions, including the regulation of actin reorganization and cell motility. MYO18A contains several functional motifs that are retained in MYO18A-FGFR1, including an N-terminal PDZ (PSD-95/Dlg/ZO-1) protein-protein interaction domain, a myosin head domain and a region that is predicted to

form multiple coiled-coils. Some of these coiled-coils could drive oligomerization of MYO18A-FGFR1, with consequent constitutive activation of the FGFR1 kinase activity.

Recently, MYO18A has also been found fused to PDGFRB as consequence of a t(5;17)(q33-q34;q11) but with a different breakpoint in which all the predicted coiled-coil domains of normal MYO18A are retained in the chimeric protein (Walz et al., 2009).

### **CPSF6**

#### **Location**

12q15

#### **Protein**

The protein encoded by CPSF6 is the 68 kD subunit of a cleavage factor required for 3' RNA cleavage and polyadenylation processing. Unlike other partners of FGFR1, CPSF6 does not have any identifiable oligomerisation motifs. However RNA recognition motifs (RRM) such as the one retained in CPSF6-FGFR1, could mediate the dimerization needed for constitutive activation of the CPSF6-FGFR1 kinase activity.

### **LRRFIP1**

#### **Location**

2q37.3

#### **Protein**

LRRFIP1 (Leucine-rich repeat Flightless-Interacting Protein 1) is a ubiquitously expressed gene that encodes for a nuclear and cytoplasmic protein with multiple functions. In the nucleus, it acts as a transcriptional repressor that decreases the expression of EGFR, PDGFRA and TNF. In the cytoplasm, it interacts with actin-binding proteins. It has an N-terminal coiled-coil domain that, as other FGFR1 partners, could drive the dimerization of LRRFIP1-FGFR1 leading to the constitutive activation of the kinase activity.

## **Result of the chromosomal anomaly**

### **Hybrid gene**

#### **Detection**

Methods of detection

1. Conventional cytogenetics to identify translocations or other rearrangements involving 8p11.
2. Fluorescent in situ hybridization (FISH) with probes flanking or covering FGFR1 to demonstrate disruption of this gene.
3. 5' RACE PCR to identify FGFR1 partner gene.
4. RT-PCR with primers located in both genes fused.

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