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Gene Section
Review

EWSR1 (Ewing sarcoma breakpoint region 1)

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Identity

Other names: EWS

HGNC (Hugo): EWSR1

Location: 22q12.2

DNA/RNA

Description

Spans 32.5 kb, in a centromere to telomere direction on plus strand; transcript of 2654 bp from 17 exons for the canonical form, with a coding sequence of 1971 nt.

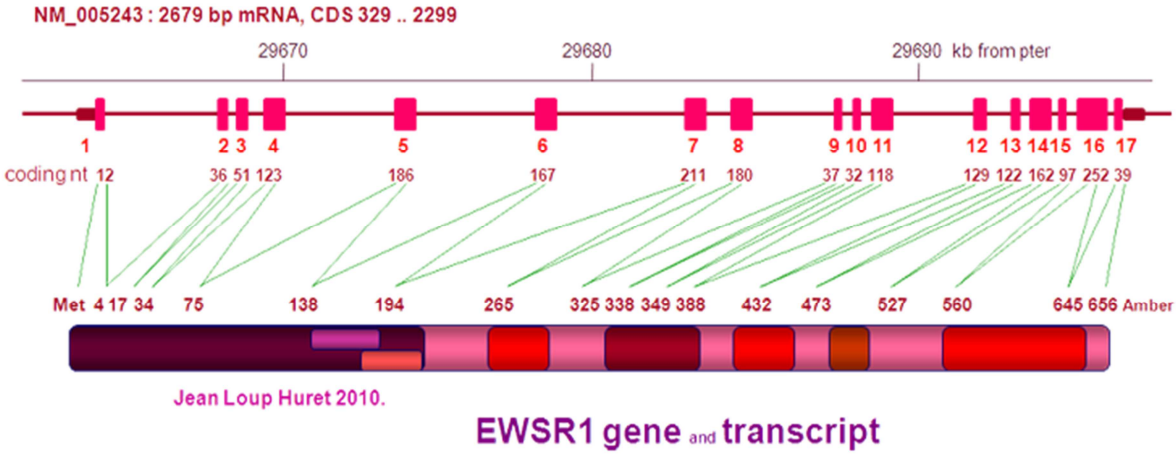
Transcription

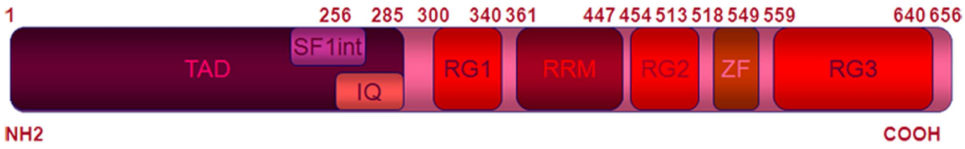
According to Ensembl, there are 25 transcripts, of which 16 different transcripts code for proteins.

Protein

Description

656 amino acids for the canonical form identified in 1993 (Plougastel et al., 1993), 68.5 kDa. From N-term to C-term: a transactivation domain (TAD) containing multiple degenerate hexapeptide repeats (consensus SYGQQS) (glycine, glutamine, serine, tyrosine rich or SYGQ rich, where the tyrosine is mandatory): amino acids 1 to 285, with a site interacting with SF1 from aa 228 to 264 and an IQ domain, which binds calmodulin (aa 256-285), 3 arginine/glycine rich domains (RGG regions) (aa 300-340, 454-513 (arginine/glycine/proline rich), and aa 559-640), a RNA recognition motif (RRM or RNA-binding domain (RBD): aa 361-447), and a RanBP2 type Zinc finger (aa 518-549).





TAD: transactivation domain (glycine/glutamine/serine/tyrosine "SYGQ" rich): amino acids 1-285
SF1int: interaction with SF1: aa 228-264
IQ: IQ domain; binds calmodulin: aa 256-285
RG1: arginine/glycine rich: aa 300-340
RRM: RNA recognition motif: aa 361-447
RG2: arginine/glycine/proline rich: aa 454-513
ZF: Zinc finger (RanBP2 type): aa 518-549
RG3: arginine/glycine rich: aa 559-640

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EWSR1 protein

Expression

EWSR1 is ubiquitely expressed (Alliegro and Alliegro, 1996; Andersson et al., 2008). In particular, EWSR1 is required for cell survival in the central nervous system (Azuma et al., 2007).

Localisation

Mainly in the nucleus. It has also been found in the cytoplasm, and associated with the plasma membrane. Expression of EWSR1 in the various subcellular compartments is affected by the methylation state of its RNA-binding domain (Belyanskaya et al., 2003).
EWSR1 is mainly found in the nucleus, and more rarely in the cytoplasm than its two homologs FUS and TAF15; the 3 proteins participate in nucleo-cytoplasmic shutlling; EWSR1 localized poorly in stress granules when cells were exposed to environmental stress (stress granules are cytoplasmic particles composed of translation pre-initiation complexes, mRNAs and RNA-binding proteins) (Andersson et al., 2008), in Cajal bodies, and nucloli. Localization of EWSR1 in different subcellular compartments reflects a dynamic distribution during cell cycle: predominant nuclear localization in interphase cells, perichromosomal localization in prometaphase cells, and cytoplasmic localization in metaphase cells, association with microtubules in quiescent cells (Leemann-Zakaryan et al., 2009).

Function

RNA binding protein, single strand DNA binding.
Role in transcriptional regulation for specific genes and in mRNA splicing: Transcription and pre-mRNA slicing, a post-transcriptional activity, are closely related.
EWSR1 plays a role in transcription initiation: EWSR1 is able to associate with the basal transcription factor TFIID (a multiprotein complex composed of the TATA-binding protein (TBP) and TBP-associated factors ($TAF_{II}s$)) and the RNA polymerase II complex. EWSR1 acts as a transcriptional activator (Bertolotti et al., 1998). It associates with heterogeneous RNA-binding proteins (hnRNPs), such as RBM38 and RBM39 (RNA binding motif proteins 38 and 39, 20q13 and 20q11 respectively) (Zinszner et al., 1994).
EWSR1 associates with EP300 and CREBBP. EWSR1 functions as a co-activator of CREBBP-dependent transcription factors. EWSR1-EP300/CREBBP mediates FOS activation, as well as HNF4 genes activation (Rossow and Janknecht, 2001; Araya et al., 2003). CREBBP is a transcription co-activator which enables the interaction between various transcription factors and RNA Pol II, brings enzymes to the promoter, and remodels the chromatin favouring the open status (Gervasini, 2009).
EWSR1 also activates other transcription factors such as POU4F1 (or BRN3A, 13q13) (Gascoyne et al., 2004), POU5F1 (or OCT4, 6p21) (Lee et al., 2005).
SF1 (splicing factor 1, 11q13, also called ZFM1) represses the transactivation domain of EWSR1; SF1, a transcription activator or repressor involved with many pathways, may negatively modulate transcription of target genes coordinated by EWSR1 (Zhang et al., 1998).
EWS functions as a docking molecule by recruiting serine-arginine (SR) splicing factors such as SRSF10 (serine/arginine-rich splicing factor 10, 1p36, or TASR, which represses pre-mRNA splicing) to RNA Pol II, coupling gene transcription to RNA splicing by binding to hyperphosphorylated RNA Pol II through its N-term part domain, and SR splicing factors through its C-term domain (Yang et al., 2000).
YBX1 (Y box binding protein 1, 1p34), a multifunctional protein that shuttles between the cytoplasm (where it binds to mRNA and regulates mRNA translation) and the nucleus (where it regulates transcription of diverse target genes), interacts with the C-term domain of EWS. This interaction docks YBX1 to RNA Pol II to participate in pre-mRNA splicing (Chansky et al., 2001).
SMN1 (survival of motor neuron 1, telomeric, 5q13) plays a major role in the pre-mRNA splicing machinery

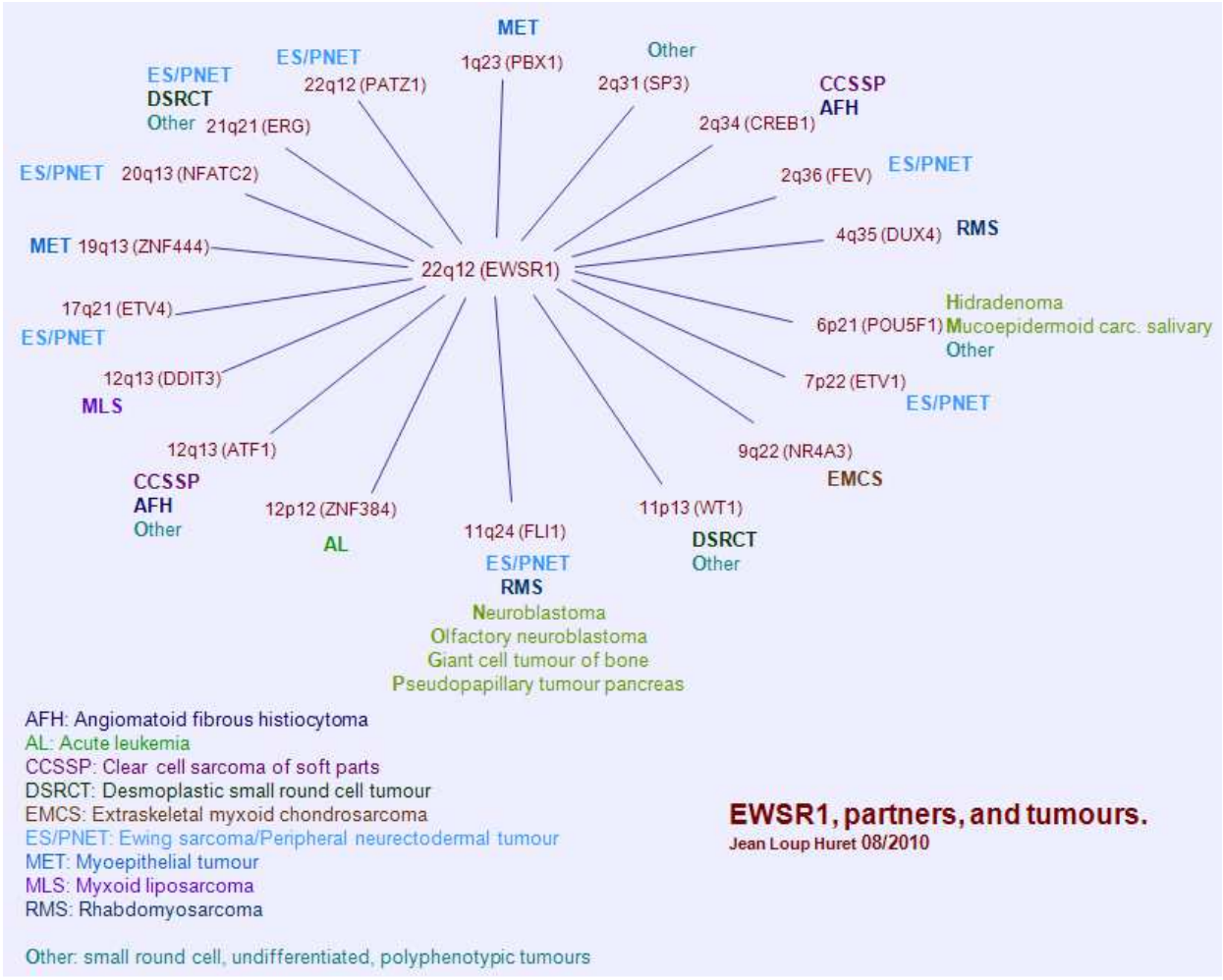
(role in spliceosomal snRNP assembly in the cytoplasm and in pre-mRNA splicing in the nucleus) (Pellizzoni et al., 1998). SMN1, through its Tudor region, binds the RG1 region of EWSR1 (Young et al., 2003).
RNU1-2 (RNA, U1 small nuclear 2, 1p36, also called U1C), another splicing protein, also interacts with EWSR1 (Knoop and Baker, 2000).
EWSR1 is phosphorylated by PRKC (protein kinase C) though its IQ domain, which inhibits RNA binding of EWSR1; CALM (calmodulin) binding to EWSR1 inhibits PRKC phosphorylation (Deloulme et al., 1997).
EWSR1 interacts with POU4F2 (4q31), a gene which regulates differentiation of neuronal cells (Gascoyne et al., 2004). EWSR1 interacts with LMNA (lamin A/C, 1q22, a component of the nuclear envelope which interacts with DNA, histones and transcriptional repressors) is essential for pre-B lymphocyte development and, during meiosis, in XY pairing and in meiotic recombination, as cross-overs are reduced in ews-/- spermatocytes. Loss of EWSR1 results in premature cellular senescence (Li et al., 2007). EWSR1 is required for proper localization of aurora B during mitosis, and maintains mitotic spindle integrity (Azuma et al., 2007).
It also interacts with BARD1 (BRCA1 associated RING domain 1) (Spahn et al., 2002).
EWSR1 and CCNL1 (cyclin L1, 3q25), are interacting partners of TFIP11 (tuftelin-interacting protein 11, 22q12), a protein functionally related to the spliceosome and involved in pre-mRNA splicing) (Tannukit et al., 2008).

Homology

Member of the TET family of RNA binding proteins, with FUS (TLS) and TAF15 (TAFII68). TET is for **T**ls, **E**wsr1, **T**afII68). TET proteins contain specific structural domains not found elsewhere in other RNA binding proteins, i.e. a N-term SYGQ rich (TAD: transactivation domain), a conserved RNA-binding domain (RRM: RNA recognition motif), RG rich regions, and a Cys_2-Cys_2 Zinc finger which can bind nucleic acids; they are also functionally related (reviews in Law et al., 2006; Tan and Manley, 2009).

Implicated in

Various tumours (see details below)



Ewing's sarcoma/Peripheral neurectodermal tumour (ES/PNET)

Note

- With: t(11;22)(q24;q12) --> FLI1 - EWSR1 (Delattre et al., 1992; Bailly et al., 1994; Thomas et al., 1994; records in the Mitelman Database).
- With: t(2;22)(q36;q12) --> FEV - EWSR1 (Llombart-Bosch et al., 2000; Peter et al., 2001; Navarro et al., 2002; Hattinger et al., 1999; Wang et al., 2007).
- With: t(7;22)(p22;q12) --> ETV1 - EWSR1 (Jeon et al., 1995; Peter et al., 2001; Zielenska et al., 2001; Wang et al., 2007).
- With: t(17;22)(q21;q12) --> ETV4 - EWSR1 (Kaneko et al., 1996; Urano et al., 1996; Urano et al., 1998).
- With: t(20;22)(q13;q12) --> NFATC2 - EWSR1 (Szuhai et al., 2009).
- With: t(21;22)(q21;q12) --> ERG - EWSR1 (Dunn et al., 1994; Giovannini et al., 1994; Kaneko et al., 1997; Maire et al., 2008; Minoletti et al., 1998; Sorensen et al., 1994; Zoubek et al., 1994; Zucman et al., 1993b; Shing et al., 2003; Peter et al., 1996).
- With: inv(22)(q12q12) --> PATZ1 - EWSR1 (Mastrangelo et al., 2000)

Note: Rare cases of ES/PNET have been described without EWSR1 involvement, but, instead:

- with: t(2;16)(q35;p11) --> FUS - FEV (Navarro et al., 2002) or,
- with: t(16;21)(p11;q22) --> FUS - ERG (Shing et al., 2003; Berg et al., 2009). To be noted that the same t(16;21)(p11;q22) has been found in rare cases of acute myeloid leukaemia.

A t(11;22)(q24;q12) has also been found in a case of cerebellar PNET (Jay et al., 1996).

Disease

Ewing's sarcoma/Peripheral neurectodermal tumour spectrum is a group of sarcomas with small blue round cells with more (PNET side) or less (Ewing side) features of neuroectodermal differentiation. ES/PNET entity also includes peripheral neuroepithelioma and Askin tumour. These tumours display both mesenchymal stem cell and neural crest stem cell properties. It is mainly found in adolescents and young adults. Cytogenetics and immunochemistry are essential for the differential diagnosis with other sarcomas (review in Romeo and Dei Tos, 2010).

Prognosis

Prognosis has dramatically improved, from less than 10% of long survivors, to a 5-year disease free survival of 75% for patients with a localized disease, and 25-30% for those with a metastatic disease (Ludwig, 2008).

Cytogenetics

The t(11;22)(q24;q12) EWSR1/FLI1 is found in 85% of cases of Ewing tumours. The t(21;22)(q21;q12) with EWSR1/ERG is the second in frequency, found in about 10% of cases.

Hybrid/Mutated gene

t(11;22)(q24;q12): 5' EWSR1 - 3' FLI1; breakpoints clustered over a 2-3 kb genomic region and over a 30-40 kb genomic region. Various junctions between EWSR1 exon 7 or 10 with FLI1 exon 5, 6, or 8. In the most common fusion type (type 1), EWSR1 exon 7 is fused in frame to FLI1 exon 6; in type 2, EWSR1 exon 7 is fused in frame to FLI1 exon 5. (Obata et al., 1999; de Alava et al., 1998).

t(21;22)(q21;q12): 5' EWSR1 - 3' ERG; the orientation of the ERG gene is from telomere to centromere, opposite to that demonstrated for EWSR1.

Other translocations: 5' EWSR1 - 3' FEV; 5' EWSR1 - 3' ETV1; 5' EWSR1 - 3' ETV4; 5' EWSR1 - 3' NFATC2; 5' EWSR1 - 3' PATZ1.

Abnormal protein

t(11;22)(q24;q12): oncogenic protein on the der(22) chromosome generated by fusion of the N terminal domain of EWSR1 protein (transactivation domain, e.g. fusion of EWSR1 amino acids 1-265) with the DNA binding domain (ETS type, amino acids 281-361) of the human FLI1 protein, a 452 amino acids protein (e.g. fusion from amino acids 260).

t(21;22)(q21;q12): oncogenic protein on the der(22) chromosome generated by fusion of the N terminal domain of EWSR1 protein with DNA binding domain of human ERG protein.

Other translocations: Most of the EWSR1 partners in ES/PNET are ETS family members (FLI1, ERG, ETV1, ETV4, FEV) and translocation results in the juxtaposition of the transactivation domain of EWSR1 with the DNA binding domain -ETS type of the partner. PATZ1 is a transcription regulator with a AT hook (DNA-binding motif), a POZ domain (mediates dimerisation) and Zn fingers (DNA-binding). NFATC2 is a cytokine inducer; translocates into the nucleus to regulate transcription.

Oncogenesis

EWSR1-FLI1 is a dominant oncogene transformed cells by subverting normal transcriptional controls/FLI1 member of ETS family. The target gene repertoire of EWSR1-FLI1 varies according to the host cell type. EWSR1-FLI1 induces a TP53-dependent growth arrest in fibroblasts, supporting the importance of TP53 loss in the genesis of Ewing's tumours (Lessnick et al., 2002). EWSR1-FLI1 activates CASP3 and promotes apoptosis in mouse embryonic fibroblasts (Sohn et al., 2010). EWSR1-FLI1 induces expression of the embryonic stem cell genes OCT4, SOX2, and NANOG in paediatric mesenchymal stem cells but not in adult mesenchymal stem cells. SOX2 is a target for EWSR1-FLI1 and miRNA145 and may be critical in Ewing sarcoma pathogenesis (Riggi et al., 2010). EWSR1-FLI1 expression in a rhabdomyosarcoma cell line induced upregulation of many genes involved in neural crest differentiation, and the cell phenotype was modified, resembling ewing tumour cells (Hu-

Lieskovan et al., 2005; Riggi et al., 2008). EZH2 is a target of EWSR1-FLI1. EZH2 regulates stemness and genes involved in neuroectodermal and endothelial differentiation (Richter et al., 2009). EWSR1-FLI1 induced T-cell neoplasia in committed lymphoid cells, showing that the oncogenetic potential of EWSR1-FLI1 is not restricted to pluripotent progenitors or mesenchymal cells (Codrington et al., 2005). EWSR1-FLI1 in transgenic mouse induced limb developmental defects by disruption of the normal development of connective tissues; homozygous deletion of p53 in mice provoke sarcomas, in particular osteosarcomas, introduction of EWSR1-FLI1 changed the tumour phenotype from osteosarcomas to poorly differentiated sarcomas (Lin et al., 2008). It is believed that EW/PNET arise from mesenchymal stem cells in which terminal differentiation is blocked by EWSR1-FLI1 (Tirode et al., 2007).

Transcriptional repressors such as NKX2-2 (Smith et al., 2006) or NR0B1 are induced by EWSR1-FLI1. Furthermore, EWSR1-FLI and NR0B1 physically interact (Kinsey et al., 2009). The transcriptional complex of EWSR1-FLI1 includes RNA polymerase II, CREB1 (cAMP responsive element binding protein 1) and DHX9 (RHA, RNA helicase A) (Toretsky et al., 2006; Erkizan et al., 2009). EWSR1-Ets proteins cooperatively bind DNA with FOS-JUN (Kim et al., 2006). EWSR1-FLI1 is involved in the spliceosome (review in Erkizan et al., 2010). EWSR1-FLI1 chimeric protein, but not wild EWSR1, can oppose the change in splicing pattern induced by expression of hnRNPA1 (Knoop and Baker, 2001).

EWSR1-FLI1 (dis)regulates many pathways (Jedlicka, 2010). CD99, a transmembrane protein highly expressed in Ewing sarcoma cells, has a key role in various biological functions, including inhibition of neuronal differentiation that may occur through the RAS/RAF/MAPK pathway in Ewing's tumours (Rocchi et al., 2010). PDGFC (Zwerner and May, 2001) as well as IGF1 are induced by EWSR1-FLI1, and also by EWSR1-ERG or FUS-ERG (Cironi et al., 2008). GLI1 is upregulated by EWSR1-FLI1, independently of the Hedgehog pathway (Beauchamp et al., 2009; Joo et al., 2009). Expression of DKK1 (which antagonizes Wnt signaling) is inhibited by EWSR1-FLI1 (Navarro et al., 2010), and DKK2 enhanced (Miyagawa et al., 2009). TGFbR2 is inhibited by EWSR1-FLI1 (Hahm, 1999).

Other features were summarized in Janknecht et al., 2005: EWSR1-FLI1 induces proliferation independent of exogenous growth factors (EWSR1-ETS proteins upregulate PDGFC and also CCND1), evasion of growth inhibition (downregulation of TGFbR2 may help cells escape growth surveillance), suppression of differentiation (ID2, overexpressed in Ewing tumours, is able to suppress differentiation of a variety of cells), immortality (hTERT (human telomerase reverse transcriptase)), limiting factor for telomerase activity and senescence, is upregulated by EWSR1-ETS fusion proteins), escape from apoptosis (EWSR1-FLI1 was shown to repress IGFBP-3, preventing apoptosis) (Janknecht et al., 2005).

Desmoplastic small round cell sarcoma (DSRCT)

Note

- With: t(11;22)(p13;q12) --> WT1 - EWSR1 (Ladanyi and Gerald, 1994; Gerald et al., 1995; Benjamin et al., 1996; records in the Mitelman Database).
- With: t(21;22)(q21;q12) --> ERG - EWSR1 (Ordi et al., 1998).

Disease

Desmoplastic small round cell sarcoma is a small blue round cells tumour, often intra-abdominal, with a male predominance, arising in children and young adults, with a very poor prognosis. Cytogenetics and immunochemistry are essential for the differential diagnosis with other sarcomas with small blue round cells.

Cytogenetics

Most of the cases are cases of t(11;22)(p13;q12).

Hybrid/Mutated gene

t(11;22)(p13;q12): 5' EWSR1 - 3' WT1; breakpoints: between EWSR1 exons 7 and 8 and between WT1 exons 7 and 8.
t(21;22)(q21;q12): 5' EWSR1 - 3' ERG.

Abnormal protein

Transcription activator.

Oncogenesis

N terminal domain of EWSR1 fused to the Zn fingers of WT1.

Clear cell sarcoma of soft parts/malignant melanoma of soft parts (CCSSP)

Note

- With: t(2;22)(q34;q12) --> CREB1 - EWSR1 (Antonescu et al., 2006; Wang et al., 2009).
- With: t(12;22)(q13;q12) --> ATF1 - EWSR1 (Zucman et al., 1993a; records in the Mitelman Database).

Disease

Clear cell sarcoma of tendons and aponeuroses affects young adults. It is characterized by slow progression, with recurrences and metastases, with only 40-50% long survivors.

Hybrid/Mutated gene

5' EWSR1 - 3' ATF1 (t(12;22)(q13;q12) cases) or, more rarely, 5' EWSR1 - 3' CREB1 (t(2;22)(q33;q12) cases).

Abnormal protein

N terminal domain of EWSR1 fused to the bZIP domain of CREB1 or ATF1.

Angiomatoid fibrous histiocytoma (AFH)

Note

- With: t(2;22)(q34;q12) --> CREB1 - EWSR1 (Antonescu et al., 2007; Shao et al., 2009; Rossi et al., 2007).
- With: t(12;22)(q13;q12) --> ATF1 - EWSR1 (Dunham et al., 2008; Hallor et al., 2005; Hallor et al., 2007; Rossi et al., 2007; Tanas et al., 2010).

Note: Cases of t(12;16)(q13;p11) with 5' FUS - 3' ATF1 have also been described (Raddaoui et al., 2002; Waters et al., 2000).

Disease

Angiomatoid fibrous histiocytoma is a rare soft-tissue tumour of low metastatic potential (local recurrence below 15% of cases, and metastases occur in less than 2% of patients); it is mostly found in children and young adults. Surgical excision is the treatment of choice.

Hybrid/Mutated gene

5' EWSR1 - 3' ATF1 (t(12;22)(q13;q12) cases), or 5' EWSR1 - 3' CREB1 (t(2;22)(q33;q12) cases).

Abnormal protein

N terminal domain of EWSR1 fused to the bZIP domain of ATF1 or CREB1.

Extraskeletal myxoid chondrosarcoma (EMCS)

Disease

Extra-skeletal myxoid chondrosarcomas represent about 5% of chondrosarcomas. There is male predominance. It affects adults mainly, in the forties or the fifties. The estimated 5-, 10-, and 15-year survival rates were 90%, 70%, and 60%, respectively (Meis-Kindblom et al., 1999).

Cytogenetics

t(9;22)(q22;q12) --> NR4A3 - EWSR1 (Labelle et al., 1995; Brody et al., 1997).

Note: Cases of t(3;9)(q12;q31) --> NR4A3 - TFG (Hisaoka et al., 2004), t(9;15)(q31;q21) --> NR4A3 - TCF12 (Sjögren et al., 2000), t(9;17)(q22;q11) --> NR4A3 - TAF15 (Sjögren et al., 1999; Attwooll et al., 1999; records in the Mitelman Database) have also been reported.

Hybrid/Mutated gene

5' EWSR1 - 3' NR4A3 (NR4A3 is also known as TEC or CHN).

Myxoid liposarcoma/round cell liposarcoma (MLS)

Disease

Myxoid liposarcoma is the most frequent type of liposarcoma, found in about half of the cases. It occurs in male and female patients equally, in their thirties to fifties. It has a relatively favorable prognosis; the variant round cell liposarcoma is much more aggressive.

Cytogenetics

A t(12;22)(q13;q12) --> DDIT3 - EWSR1 (Panagopoulos et al., 1994) is found in 5% of cases, whereas a t(12;16)(q13;p11) is found in most cases.

Hybrid/Mutated gene

5' EWSR1 - 3' DDIT3 (also called CHOP). The t(12;16)(q13;p11) with 5' FUS - 3' DDIT3 is more frequent.

Abnormal protein

Fuses the N-term transactivation domain of EWSR1 with the bZIP domain of DDIT3.

Acute leukaemia

Disease

Acute lymphoblastic leukaemia (B-cell ALL), biphenotypic leukaemia

Cytogenetics

A t(12;22)(p13;q12) was found in 2 cases (Martini et al., 2002). Note: the equivalent t(12;17)(p13;q11) --> TAF15 - ZNF384 has also been found in other cases of the same series.

Hybrid/Mutated gene

5' EWSR1 - 3' ZNF384.

Abnormal protein

Fuses the N-term transactivation domain of EWSR1 with the leucine-serine rich-proline-nuclear localization signal-Kruppel-type C2H2 Zinc finger domains of ZNF384.

Note

EWSR1 involvement has also been described in a number of other tumours. In some instances, the diagnosis is unambiguous; in other cases, pathological diagnoses are difficult to reach, when the tumour is undifferentiated or polyphenotypic.

Rhabdomyosarcoma (RMS)

Disease

Rhabdomyosarcomas, the most common pediatric soft tissue sarcomas, are tumours related to the skeletal muscle lineage. The 2 major subtypes are alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS). Most ARMS cases are

characterised by either a t(2;13)(q35;q14), resulting in a PAX3 - FOXO1 hybrid gene, or a t(1;13)(p36;q14) resulting in a PAX7 - FOXO1 hybrid gene (Reichek and Barr, 2009).

However, 4 cases of RMS have been described, instead, with an EWSR1 rearrangement.

Cytogenetics

A t(4;22)(q35;q12) was found in a case of embryonal rhabdomyosarcoma (Sirvent et al., 2009), and a t(11;22)(q24;q12) in the other cases (Sorensen et al., 1993; Thorner et al., 1996).

Hybrid/Mutated gene
5' EWSR1 - 3' DUX4 in the t(4;22)(q35;q12) case, and 5' EWSR1 - 3' FLI1 in the t(11;22) cases.

Giant cell tumour of bone

Disease
Locally destructive tumour, usually seen in patients over 20 years of age, with good prognosis, despite of recurrences and pulmonary metastases (Forsyth and Hogendoorn, 2003).

Cytogenetics
In giant-cell tumour of bone, the most frequent finding is telomeric association. One study showed that a very minor clone with EWSR1/FLI1 translocation could be detected in most of the cases studied (Scotlandi et al., 2000).

Hybrid/Mutated gene
5' EWSR1 - 3' FLI1.

Myoepithelioma/myoepithelial carcinoma of soft parts

Disease
Myoepithelioma tumours of soft tissue cover a wide range of tumours of various behaviour. While most are of intermediate aggressivity, some metastase.

Cytogenetics
t(1;22)(q23;q12) in one case (Brandal et al., 2008), t(19;22)(q13;q12) in another case (Brandal et al., 2009).

Hybrid/Mutated gene
5 ' EWSR1 - 3' PBX1, which fuses exons 8 from EWSR1 to exons 5 of PBX1 in the most benign case; 5' EWSR1- 3' ZNF444 in the malignant case; fuses EWSR1 exon 8 to the very near end of ZNF444.

Hidradenoma of the skin

Disease
Hidradenoma or eccrine/apocrine acrospiroma, is a benign adnexal tumour developing most often in adults. 3 cases were found with a t(6;22)(p21;q12) and/or its fusion transcript equivalent (Möller et al., 2008).

Abnormal protein
5' EWSR1 - 3' POU5F1.

Mucoepidermoid carcinoma of the salivary glands

Disease
Mucoepidermoid carcinoma is the most common type of malignant salivary gland tumour, often associated with a t(11;19)(q21;p13) translocation with expression of chimeric genes 5' CRTC1 - 3' MAML2. One case of mucoepidermoid carcinoma was found with a t(6;22)(p21;q12) (Möller et al., 2008).

Abnormal protein
5' EWSR1 - 3' POU5F1.

Neuroblastoma

Disease
Neuroblastomas are peripheral neuroblastic tumours derived from cells of the sympathetic nervous system. They occur mainly in infants and young children, with a median age of 1.5 years.

Hybrid/Mutated gene
Two patients, aged 3 years and 5.5 years, were described with a 5' EWSR1 - 3' FLI1 transcript in typical neuroblastomas with elevated urinary catecholamines. Prognosis had been very poor: the two patients relapsed during -or at the end of- treatment and died within 2 months (Burchill et al., 1997).

Olfactory neuroblastoma

Disease
Olfactory neuroblastoma or esthesioneuroblastoma, is a malignant neurectodermal tumour, from the olfactory neuroepithelium that typically occurs in the superior nasal cavity. It is keratin negative, neuroendocrine marker positive, and S100 positive. It arises at any age, often in the adult, with a 5-year survival rate above 50% (the 5-year overall survival for patients treated for nonmetastatic olfactory neuroblastoma was recently found at 64% (Ozsahin et al., 2010)).

Cytogenetics
t(11;22)(q24;q12), inducing a 5' EWSR1 - 3' FLI1 hybrid gene (Sorensen et al., 1996). However, recent review rejects cases with EWSR1 involvement, as being misdiagnosed cases of ES/PNET (Thompson, 2009).

Solid pseudopapillary tumour of the pancreas (SPTP)

Disease
Solid pseudopapillary tumour of the pancreas is a rare epithelial tumour, typically occuring in young female patients, rarely metastasizing (Yu et al., 2010).

Cytogenetics
One case showed a t(11;22)(q24;q12) (Maitra et al., 2000)

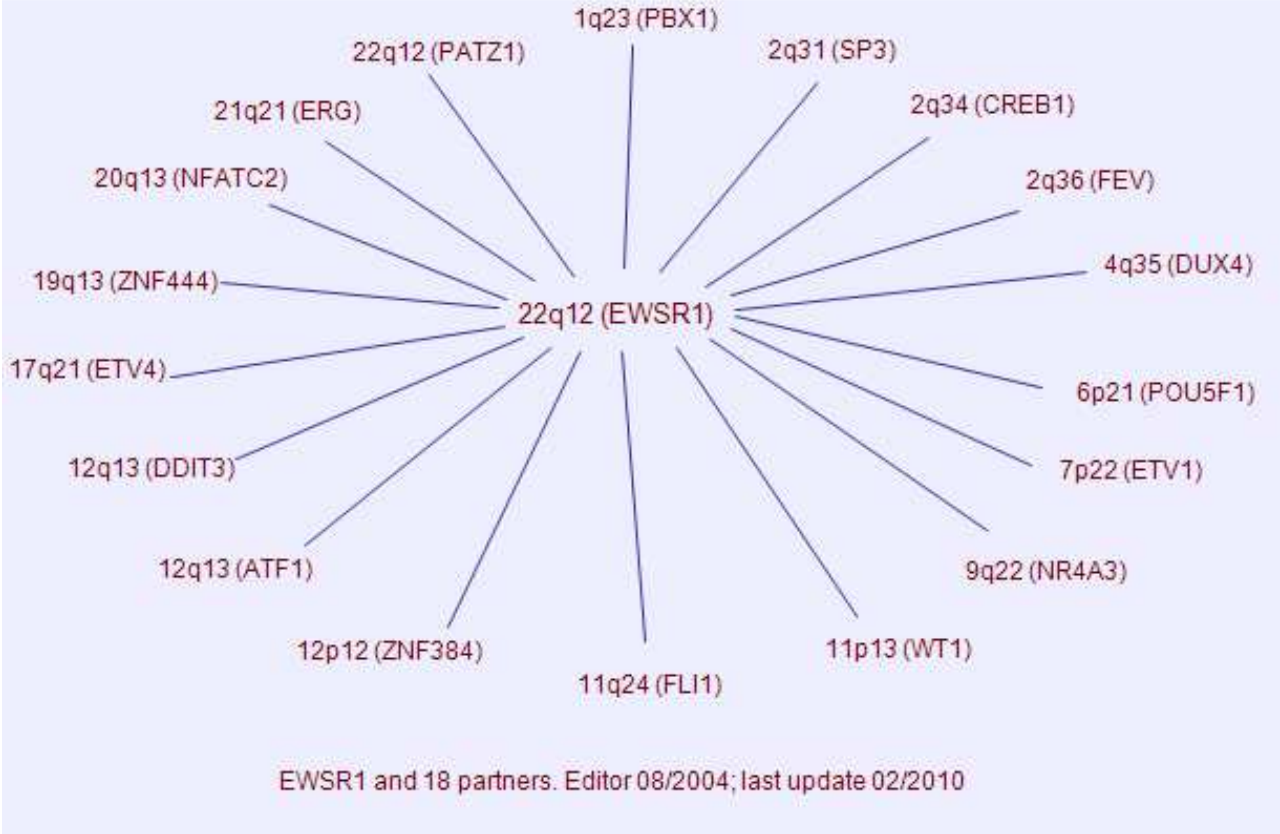
Hybrid/Mutated gene
5' EWSR1 - 3' FLI1.

"Small round cell tumours", "polyphenotypic mesenchymal malignancies", and "undifferentiated sarcomas"

Disease
An undifferentiated sarcoma derived from pelvic bone exhibited a t(6;22)(p21;q12) with 5' EWSR1 - 3' POU5F1. This resulted in the fusion of exons 1-6 of EWSR1 and exons 2-5 and a part of exon 1 of POU5F1.The patient died 6 months after diagnosis (Yamaguchi et al., 2005).

A small round cell tumour was found to have a t(2;22)(q31;q12), with 5' EWSR1 - 3' SP3 hybrid gene; fuses the exon 7 of EWSR1 to exon 6 of SP3. N-term transactivation domain of EWSR1 fused with the Zinc fingers of SP3. The patient died 20 months after diagnosis (Wang et al., 2007).
Other cases of spindle cell tumours, small round cell poorly differentiated, biphenotypic (myogenic/neural differentiation), or polyphenotypic sarcomas present with the classical t(11;22)(q24;q12) / 5' EWSR1 - 3' FLI1 or other variants, such as the t(2;22)(q36;q12) / 5' EWSR1 - 3' FEV (Wang et al., 2007), the t(11;22)(p13;q12) / 5' EWSR1 - 3' WT1 (Alaggio et al., 2007), the t(12;22)(q13;q12) / 5' EWSR1 - 3' ATF1 (Somers et al., 2005), or the t(21;22)(q21;q12) / 5' EWSR1 - 3' ERG (Tan et al., 2001).

Breakpoints



Note
Clustered over a 2.3 kb genomic region.

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