Soft tissue tumors: t(1;13)(p36;q14) in alveolar rhabdomyosarcoma

Frederic G Barr

Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA (FGB)

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Clinics and pathology

Phenotype / cell stem origin
Generally found in alveolar rhabdomyosarcoma (ARMS); also found in rare cases diagnosed as embryonal rhabdomyosarcoma (ERMS).

Epidemiology
Occurs in ~20% ARMS cases and <5% of ERMS cases: patients tend to be younger children compared to those with t(2;13)-positive ARMS tumors.

Clinics
Tumors tend to show lower invasiveness compared to those with t(2;13)-positive ARMS tumors. In metastatic cases, there is a low incidence of bone marrow involvement.

Prognosis
In one study, patients with localized t(2;13) and t(1;13)-positive ARMS had comparable outcomes whereas a recent study with small numbers suggested that localized t(1;13) tumors had a better outcome than those with localized t(2;13) tumors. Among patients presenting with metastatic disease, those with t(1;13)-positive tumors had a significantly better outcome than those with t(2;13)-positive tumors. Note: these studies are based on molecular detection of the translocations.

Cytogenetics

Cytogenetics Morphological
Though a balanced 1;13 is sometimes visible in cases with the associated molecular fusion event, in many cases the balanced translocation is not visible. Instead the molecular fusion is found associated with a subsequent amplification event, usually double minute chromosomes.

Cytogenetics Molecular
The product of the 1;13 translocation is amplified in ~90% of t(1;13)-positive cases.

Additional anomalies
Amplification events involving 2p24 and 13q31 (as determined by DNA-based array studies).
Genes involved and proteins

**PAX7**

**Location**

1p36

**Protein**

Transcription factor - paired box (PAX) family.

**FOXO1 (FKHR)**

**Location**

13q14

**Protein**

Transcription factor - forkhead box (FOX) family.

Result of the chromosomal anomaly

**Hybrid Gene**

**Description**

The 1:13 translocation breaks within intron 7 of the PAX7 gene and intron 1 of the FOXO1 gene on chromosome 13 to generate a PAX7-FOXO1 fusion gene as well as a reciprocal FOXO1-PAX7 fusion gene. In ~55% of PAX7-FOXO1-positive ARMS tumors, this FOXO1-PAX3 gene is not detectable. In cases with fusion gene amplification, the PAX7-FOXO1 fusion gene is amplified whereas the reciprocal FOXO1-PAX7 fusion gene is not.

**Transcript**

The PAX7-FOXO1 fusion transcript consists of the first 7 exons of PAX3 fused to FOXO1 exons 2 and 3. There is evidence that the PAX7-FOXO1 fusion transcript is upregulated relative to the wild-type PAX7 transcript, presumably due to increased copy number of the fusion gene by amplification.

**Fusion Protein**

**Description**

The fusion gene has a 2484 nt open reading frame encoding an 828 amino acid fusion protein. This fusion protein is a transcription factor with a PAX7 DNA binding domain and FOXO1 transactivation domain.

**Expression / Localisation**

Nuclear.

**Oncogenesis**

Transcription dysregulation. At the cellular level there is evidence of alterations in control of growth. In conjunction with other genetic changes, recipient cells show transformation in culture and tumorigenesis in injected mice.

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