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Solid Tumour Section

Short Communication

Mesothelioma: t(14;22)(q32;q12) in mesothelioma

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Identity

Mesothelioma is an aggressive tumor derived from mesothelial cells. It is primarily found in the pleura (75%), peritoneum (10-20%), pericardium (1%) and tunica vaginalis (< 1%) (Moore et al., 2008). Mesothelioma is strongly associated with exposure to asbestos which can be documented in about 50-80% of pleural cases and 30% of peritoneal mesothelioma in men (Bianchi and Bianchi, 2007). Genetic predisposition, smoking, radiation, and viral infection can also contribute to mesothelioma. The onset of mesothelioma is insidious with a latency of 30 years (range: 20 to 50 years).
The mean age of the patients is 60 years, but the disease can occur at any age (Moore et al., 2008). Survival rates vary but they generally remain low (Asbestos.com).

Clinics and pathology

Disease

Mesothelioma

Phenotype / cell stem origin

Mesothelioma is derived from mesothelial cells.

Embryonic origin

Unknown.

Etiology

Mesothelioma is strongly associated with exposure to asbestos which can be documented in about 50-80% of pleural cases and 30% of peritoneal mesothelioma in men (Bianchi and Bianchi, 2007). Genetic predisposition, smoking, radiation, and viral infection can also contribute to mesothelioma either alone or together with exposure to asbestos.

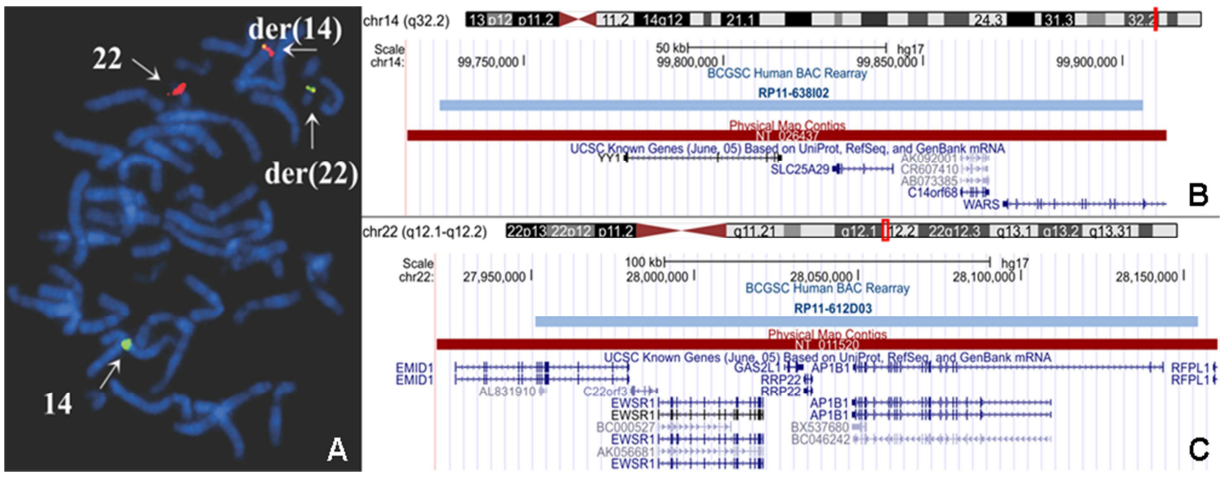
Epidemiology

For a detailed and update epidemiology of mesothelioma see: http://www.uptodate.com/contents/epidemiology-of-malignant-pleural-mesothelioma.

Genetics

Note

Abnormal karyotypes detected by cytogenetic analysis have been reported in 128 mesotheliomas (Mitelman database).
The changes are mostly complex, but a number of nonrandom abnormalities have been found involving chromosome arms 1p, 3p, 6q, 9p, and 22q. Studies using comparative genomic hybridization, loss of heterozygosity, and fluorescence in situ hybridization (FISH) have also shown repeated regional chromosomal gains and losses. Among them, losses of chromosome bands 14q32 and 22q12 were found in 43-50% and 36% of the cases, respectively (Taniguchi et al., 2007; Takeda et al., 2012). On band 22q12, the NF2 gene was found to be mutated in 40% of mesotheliomas leading to complete functional inactivation of NF2 (see Thurneysen et al., 2009; and references therein). In two other studies, NF2 was found to be deleted (Taniguchi et al., 2007; Takeda et al., 2012). On chromosome band 14q32, the CHGA and ITPK1 genes were found to be deleted (Taniguchi et al., 2007; Takeda et al., 2012).

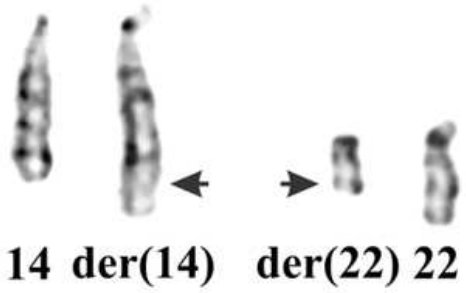


A. Fluorescence in situ hybridization using BAC RP11-638I2 (FITC, green) for the YY1 gene (14q32) and RP11-612D3 (Texas Red, red) for the EWSR1 gene (22q12). The fusion signals are seen on both derivative chromosomes. **B.** Mapping position of the RP11-638I2. **C.** Mapping position of the RP11-612D3.

Cytogenetics

Note

In a mesothelioma, which was diagnosed as epithelioid type, the G-banding analysis yielded a karyotype with only a single chromosomal abnormality:
46,XY,t(14;22)(q32;q12)[10]/46,XY[5] (Panagopoulos et al., 2013).



Partial karyotype showing the two derivative chromosomes, der(14)t(14;22)(q22;q12) and der(22)t(14;22)(q22;q12), from the 14;22 translocation together with their corresponding normal homologues; breakpoints are indicated by arrows.

Genes involved and proteins

YY1

Location

14q32.2

DNA / RNA

Spans 44.495 kb on plus strand.

Protein

414 amino acids, 44.7 kDa.

EWSR1

Location

22q12.2

DNA / RNA

Spans 32.5 kb on plus strand. Transcript of 2654 bp from 17 exons for the canonical form, with a coding sequence of 1971 nt.

Protein

656 amino acids, 68.5 kDa.

Result of the chromosomal anomaly

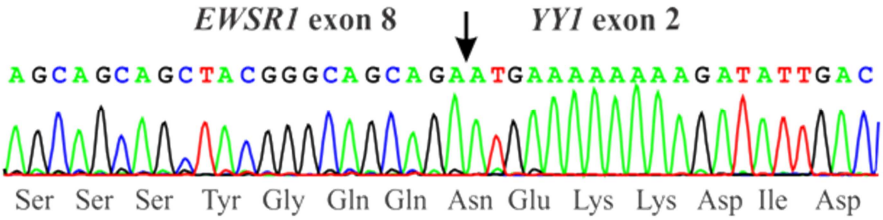
Hybrid Gene

Note

The balanced 14;22-translocation generates a functional EWSR1-YY1 chimeric gene in which exon 8 of EWSR1 (nucleotide 1139 accession number NM_013986 version 3; former exon 7 in sequence with accession number X66899) is fused to exon 2 of YY1 (nucleotide 1160 accession number NM_003403 version 3). The putative EWSR1-YY1 protein would contain the transactivation domain of EWSR1 and the DNA binding domain of YY1 and thus may act as an abnormal transcription factor.

Description

The EWSR1-YY1 fusion gene was detected in 2 so far mesotheliomas (Panagopoulos et al., 2013).



Partial sequence chromatogram showing the fusion of exon 8 of EWSR1 with exon 2 of YY1.

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