

Solid Tumour Section

Mini Review

Carcinoma with t(15;19) translocation

Anna Collin

Department of Clinical Genetics, Lund University Hospital, 221 85 Lund, Sweden

Published in Atlas Database: February 2007

Online updated version: <http://AtlasGeneticsOncology.org/Tumors/Carcinot1519q14p13ID5474.html>

DOI: 10.4267/2042/38455

This work is licensed under a Creative Commons Attribution-Non-commercial-No Derivative Works 2.0 France Licence.

© 2007 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Other names: Mediastinal carcinoma with chromosome translocation t(15;19); Midline carcinoma of children and young adults with NUT rearrangement; Midline carcinoma with t(15;19); Poorly differentiated carcinoma with t(15;19); Poorly differentiated thymic carcinoma; t(15;19) positive tumor.

Clinics and pathology

Disease

Carcinoma with t(15;19) translocation.

Phenotype stem cell origin

It has been suggested that tumor cells derive from early epithelial progenitor cells.

Embryonic origin

The majority of the cases presumably derive from various (midline) epithelial surfaces. One tumor, localized to the iliac bone and staining negative for epithelial, endothelial, germ cell and neuroendocrine markers has been reported, suggesting that the tumor might also derive from non-epithelial structures.

Etiology

Unknown.

Epidemiology

A total of 13 cases have been reported to date. All tumors occurred in children or young adults with a median age of 15 years of age (range 3-35). There seem to be no sex predilection (8 males, 5 females).

Clinics

The growth pattern is typically aggressive and locally invasive. Metastatic growth is common in particular in bone, but also in lymph nodes and lungs.

Cytology

Focal reactivity with pan-cytokeratin markers. Negative for CD30, CD45, PLAP, HMB45, S100 and neuroendocrine markers.

Pathology

The tumor cells are typically undifferentiated, of intermediate size and the mitotic index is high.

Treatment

Intensive combined chemotherapy and occasionally radiotherapy.

Prognosis

Extremely poor. Among the cases reported so far, the median survival time was 18 weeks (range 6-67).

It has been suggested that a critical prognostic difference exists between BRD4-NUT/t(15;19) positive tumors and tumors where NUT is rearranged but fused to an as yet unknown partner.

Cytogenetics

Cytogenetics morphological

The characteristic t(15;19) has been observed in all reported cases. The reported breakpoints on chromosome 15 have varied (15q11-q15). The breakpoints on chromosome 19 clustered to 19p13 in the majority of the cases. In one case the breakpoint was interpreted as 19q13.

Cytogenetics molecular

Various FISH protocols for the detection of 15q and 19p rearrangements, strongly indicating the presence of a t(15;19), have been reported. The material used has been paraffin-embedded sections of tumor biopsy or metaphase spreads of cultured tumor tissue.

Probes

Probes for NUT: RP11-194H7 covering the gene or BAC 87M17 and YAC 766E7 flanking the gene.

Probes for BRD4: RP11-637P24 covering the gene or BACs 1H8+64O3 and BACs 412E10+3D4 flanking the gene.

Additional anomalies

The t(15;19) is typically seen as the sole change. In one case a variant t(11;15;19) was reported.

Variants

t(15;?)(q14;?) leading to rearrangement and fusion of NUT to an unknown partner gene.

Genes involved and Proteins

NUT (nuclear protein in testis)

Location: 15q14 (position 32425358-32437221 on the chromosome 15 genomic sequence according to the UCSC database; assembly of May 2004)

DNA/RNA

The gene consists of 7 exons that span approximately 12 kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon and the stop codon are predicted to exon 1 and exon 7, respectively. The corresponding wildtype mRNA transcript is 3.6 kb.

Protein

The open reading frame is predicted to encode a 1127 amino acid protein with an estimated molecular weight of 120 kDa. The protein is nuclear and Northern blot analysis has indicated that the normal expression of the NUT gene is highly restricted to the testis.

BRD4 (bromodomain containing 4)

Location: 19p13 (position 15252262-15209302 on the chromosome 19 genomic sequence according to the UCSC database; assembly of May 2004).

DNA/RNA

The gene consists of 20 exons that span approximately 43 kb of genomic DNA in the centromere-to-telomere orientation. The translation initiation codon and stop codon are located to exon 2 and exon 20, respectively. Two isoforms of BRD4 have been reported. The BRD4 long isoform encodes a 6.0 kb mRNA that corresponds to the full length transcript. The BRD4 short isoform encodes a 4.4 kb mRNA that corresponds to an alternative splicing variant lacking exons 12-20.

Protein

The open reading frame encodes a 1362 amino acid protein with a molecular weight of 200 kDa. The protein is nuclear and Northern blot analysis has shown an ubiquitous normal expression of both BRD4 isoforms.

Result of the chromosomal anomaly

Hybride Gene

Description

The t(15;19)(q14;p13) results in a BRD4-NUT chimeric gene where exon 10 of BRD4 is fused to exon 2 of NUT.

Detection protocole

The hybrid gene can be visualized by FISH using gene specific probes or by RT-PCR.

Fusion protein

Description

The BRD4-NUT fusion protein is composed of the N-terminal of BRD4 (amino acids 1-720 out of 1372) and almost the entire protein sequence of NUT (amino acids 6-1127). The N-terminal of BRD4 includes bromodomains 1 and 2 and other, less well characterized functional domains.

Oncogenesis

It has been suggested that the oncogenic effect of the NUT-BRD4 fusion is caused not only by the abnormal regulation of NUT by BRD4 promotor elements but also by the consequent ectopic expression of NUT in non-germinal tissues.

References

- Kees UR, Mulcahy MT, Willoughby MLN. Intrathoracic carcinoma in an 11-year-old girl showing a translocation t(15;19). *Am J Pediatr Hematol Oncol* 1991;13:459-464.
- Kubonishi I, Takehara N, Iwata J, Sonobe H, Ohtsuki Y, Abe T, Miyoshi I. Novel t(15;19) chromosome abnormality in a thymic carcinoma. *Cancer Res* 1991;51:3327-3328.
- Lee ACW, Kwong Y-I, Fu KH, Chan GCF, Ma L, Lau Y-I. Disseminated mediastinal carcinoma with chromosomal translocation (15;19). A distinctive clinicopathologic syndrome. *Cancer* 1993;72:2273-2276.
- Dang TP, Gazdar AF, Virmani AK, Sepetavec T, Hande KR, Minna JD, Roberts JR, Carbone DP. Chromosome 19 translocation, overexpression of Notch3, and human lung cancer. *J Natl Cancer Inst* 2000;92:1355-1357.
- French CA, Miyoshi I, Aster JC, Kubonishi I, Kroll TG, Dal Cin P, Vargas SO, Perez-Atayde AR, Fletcher JA. BRD4 bromodomain gene rearrangement in aggressive carcinoma with translocation t(15;19). *Am J Pathol* 2001;159:1987-1992.
- Vargas SO, French CA, Faul PN, Fletcher JA, Davis IJ, Dal Cin P, Perez-Atayde AR. Upper respiratory tract carcinoma with chromosomal translocation 15;19. Evidence for a distinct disease entity of young patients with a rapidly fatal course. *Cancer* 2001;92:1195-1203.
- French CA, Miyoshi I, Kubonishi I, Grier HE, Perez-Atayde AR, Fletcher JA. BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. *Cancer Res* 2003;63:304-307.
- Toretzky JA, Jenson J, Sun C-C, Eskenazi AE, Campbell A, Hunger SP, Caires A, Frantz C, Hill JL, Stamberg J. Translocation t(11;15;19): a highly specific chromosome

rearrangement associated with poorly differentiated thymic carcinoma in young patients. *Am J Clin Oncol* 2003;26:300-306.

French CA, Kutok JL, Faquin WC, Toretsky JA, Antonescu CR, Griffin CA, Nose V, Vargas SO, Moschovi M, Tzortzatou-Stathopoulou F, Miyoshi I, Perez-Atayde AR, Aster JC, Fletcher JA. Midline carcinoma of children and young adults with NUT rearrangement. *J Clin Oncol* 2004;22:4135-4139.

Marx A, French CA, Fletcher JA. Carcinoma with t(15;19) translocation. In: World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, thymus, pleura and heart. Travis WD, Brambilla E, Muller-Hermelink K, Harris CC, editors. Oxford University Press 2004. pp185-186.

You J, Croyle JL, Nishimura A, Ozato K, Howley P. Interaction of the bovine papillomavirus E2 protein with Brd4 tethers the viral DNA to host mitotic chromosomes. *Cell* 2004;117:349-360.

Engleson J, Soller M, Panagopoulos I, Dahlén A, Dictor M, Jerkeman M. Midline carcinoma with t(15;19) and BRD4-NUT fusion oncogene in a 30-year-old female with response to docetaxel and radiotherapy. *BMC Cancer* 2006;6:69.

Mertens F, Wiebe T, Adlercreutz C, Mandahl N, French CA. Successful treatment of a child with t(15;19)-positive tumor. *Pediatr Blood Cancer* 2006.

This article should be referenced as such:

Collin A. Carcinoma with t(15;19) translocation. *Atlas Genet Cytogenet Oncol Haematol.* 2007;11(3):249-251.
