t(4;19)(q35;q13) in pediatric undifferentiated soft tissue sarcomas

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Identity

Other names
CIC-DUX4-positive pediatric primitive round cell sarcomas, Ewing-like sarcomas with t(4;19)(q25;q13) translocation, CIC fusion with DUX4 in EWSR1-negative undifferentiated small blue round cell sarcomas, t(4;19)(q35;13.1) in primitive mesenchymal tumors, Translocation (4;19)(q35;q13.1)-associated primitive round cell sarcomas

Clinics and pathology

Disease
Approximately 5% of sarcomas remain unclassifiable using current diagnostic techniques. These tumors, termed undifferentiated soft tissue sarcomas, show no specific lineage differentiation and exhibit no well-established immunohistochemical profile (Somers et al., 2006). Recently, a subclass of undifferentiated sarcomas with primitive round cell morphology were found to harbor a CIC-DUX4 fusion gene resulting from a t(4;19)(q35;q13) rearrangement.

Epidemiology
A total of 8 pediatric cases have been reported to date (Richkind et al., 1996; Rakheja et al., 2008; Yoshimoto et al., 2009; Graham et al., 2011; Italiano et al., 2011).

There seems to be no sex predilection as 4 patients were male and 4 patients were female. Tumors occurred in children with a median age of 11.5 years (range 6-16), with no difference between the ages of the males and females.

Clinics
Primary tumors were located in the trunk (n=4), lower extremities (n=3) and head and neck (n=1). Of the 8 patients, 3 patients died as a result of the disease and 5 were alive at last stated follow-up.

Pathology
Tumors are composed of primitive round cells arranged in sheets or nests, with increased nuclear:cytoplasmic ratios. No evidence of differentiation is discernible at the light microscopy level. The majority are positive for CD99 in either a membranous or cytoplasmic pattern of expression.

Genetics

Note
This fusion gene has been identified using various molecular genetic and cytogenetic methods including real-time polymerase chain reaction (RT-PCR), G-banding, Spectral Karyotyping (SKY) and Fluorescence in situ hybridization (FISH).
**Cytogenetics**

**Note**
This fusion gene cannot always be detected using gross cytogenetic techniques (G-banding/SKY). In at least one case, SKY did not identify the fusion gene, but subsequent FISH and RT-PCR analyses found the case to be positive for the t(4;19)(q35;q13) (Yoshimoto et al., 2009).

**Cytogenetics Molecular**

Fluorescence in situ hybridization (FISH) with probes for the CIC and DUX4 genes can be used to detect the CIC-DUX4 rearrangement, as it displays fusion of signals on one chromosome.

**Genes involved and proteins**

**CIC (capicua homolog)**

**Location**
19q13

**Protein**
The human CIC gene is an ortholog of the Drosophila capicua gene, and is a member of the HMG-box superfamily of transcription factors (Lee et al., 2002). This gene has 20 exons encoding a protein of 1608 amino acids, and contains an N-terminal DNA-binding HMG-box and sixteen possible MAPK phosphorylation sites. CIC has been shown to be involved in mediating two oncogenic signalling pathways, EGFR and Wnt, by transcriptional repression (Lee et al., 2005).

**DUX4 (double-homeobox 4)**

**Location**
4q35

**Protein**
The DUX4 gene is a double-homeobox gene belonging to the family of double homeodomain transcriptional activators. DUX4 is located within the tandem repeat locus D4Z4 on chromosome 4 and contains two DNA-binding homeoboxes at its N-terminus (Gabriels et al., 1999). A similar D4Z4 repeat has been identified on chromosome 10.

**Result of the chromosomal anomaly**

**Hybrid Gene**

**Description**
5’ CIC - 3’ DUX4. Fusion of exon 20 of the CIC gene and exon 1 of the DUX4 gene, resulting in an in-frame fusion between CIC and DUX4 with the CIC open reading frame and the DUX4 stop codon. In 5 of the 8 cases the fusion breakpoint was mapped, and 4 distinct
breakpoints within exon 20 of CIC and exon 1 of DUX4 were identified (Yoshimoto et al., 2009; Graham et al., 2011).

**Fusion Protein**

**Note**

Protein prediction suggests that this fusion leaves intact the majority of the CIC protein functional domains, including the DNA-binding high-mobility group (HMG)-box, and 15 of 16 putative MAPK phosphorylation sites, but results in the loss of the majority of the DUX4 protein functional domains, namely both DNA-binding homeodomains (Graham et al., 2011).

**To be noted**

**Note**

An additional 7 adult cases of t(4;19)(q35;q13)-positive undifferentiated soft tissue sarcomas have been reported to date (Kawamura-Saito et al., 2006; Italiano et al., 2011). Furthermore, 6 cases (1 pediatric and 5 adult) have been identified which harbor a fusion between the CIC gene on chromosome 19 and the DUX10 gene (DUX4 homolog) on chromosome 10 (Italiano et al., 2011).

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