INHERITANCE OF PAGET’S OSTEOSARCOMA OF BONE: A LOSS OF HETEROZYGOSITY STUDY

Introduction: Pagetoid osteosarcoma is a complication of Paget’s disease of bone. Sarcomatous transformation is most often seen in severe, long-standing Paget’s disease. Familial clustering of Paget’s disease has been described with apparent autosomal dominant inheritance with high penetrance by the sixth decade. Although definitive proof of the specific gene involved remains elusive, some researchers have shown loss of heterozygosity in a region of chromosome 18q in a relatively high percentage of studied patients affected with either Paget’s disease alone, in Pagetoid osteosarcoma, and in uncomplicated osteosarcoma. The index patient was diagnosed with Pagetoid osteosarcoma and had a first-degree relative with history of the same. We hypothesized that our patient’s tumor samples might contain a similar genetic abnormality.

Purpose: This study examines examines the hypothesis that loss of heterozygosity exists in a region of chromosome 18q in affected family members in a family in whom the father and son each died at a young age with Pagetoid osteosarcoma.

Materials and Methods:

Family Pedigree: The index patient, a 33-year-old male with a nine-year history of Paget’s disease involving bilateral femurs and the right tibia, was diagnosed with locally advanced stage IIb grade IV Pagetoid osteosarcoma in his right distal femur. The patient died with pulmonary metastatic disease less than two years after initial diagnosis despite appropriate treatment. The father of the index patient, at age 39, presented at Roswell Park Cancer Center in Buffalo, New York in early 1962 with bilateral distal femoral biopsy-proven Paget’s disease of bone and right femoral Pagetoid osteosarcoma. The patient was treated with hip disarticulation and succumbed to pulmonary and osseous metastatic disease less than two years later. These two are survived by the mother and three siblings of the index patient.

Results: Our analysis of several polymorphic markers from the chromosome 18q21-22 region showed loss of heterozygosity throughout the region. Loss of heterozygosity involving the maternally inherited alleles was detected in the tumor (II:5) as compared to the blood (II:4). Markers in 18q21.2 (D18S858), 18q22.1 (D18S68, D18S55, D18S1113, D18S878) were detected in reduced amounts indicating a chromosomal deletion. (Fig. 1A) The maternally inherited MBP micro-satellite allele in 18q23 did not appear to be deleted in the tumor. (Fig. 1B) Thus the distal breakpoint lies between D18S878 and MBP. The proximal breakpoint was not defined but appears to lie proximal to D18S858.

Conclusions: A putative tumor suppressor gene on chromosome 18q has been previously identified in individuals with Pagetoid osteosarcoma based upon loss of heterozygosity in the 18q21-22 region. In another study examining this region of chromosome 18q21-22 with seven polymorphic loci in eight genetically diverse families affected by Paget’s disease only, only five of the families showed linkage to this portion of the chromosome. Our results are consistent with the paternal transmission of a mutation in a putative tumor suppressor gene that is uncovered by an acquired “second hit” deletion including 18q22.1 in the tumor. The carrier status of this putative tumor suppressor mutation in the three unaffected siblings is uncertain given the lack of an exact location of the tumor suppressor and the lack of a paternal sample to genotype.

Our genetic analysis does support the idea of a susceptibility region on chromosome 18 in the region described previously. Work to definitively determine the associated gene would potentially be helpful in further understanding the disease etiology. The gene encoding the receptor activator of nuclear factor-kappa B (RANK, TNFRSF11A) lies within the critical region of 18q that has been deleted. The RANK gene represents a strong candidate gene since it has been found to be mutated in familial expansile osteolysis. Although thus far the RANK gene has not been found to be mutated in Paget’s disease of bone, Wuyts did find a statistical association between a RANK polymorphism and Paget’s disease of bone, indicating that it may represent a susceptibility factor. Sequencing of this gene in the presented family, as well as examination of other regions, including the PDB1 locus may uncover more information.

References:

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