DNA Sequence of the Translocation Breakpoints in Undifferentiated Embryonal Sarcoma Arising in Mesenchymal Hamartoma of the Liver Harboring the t(11;19)(q11;q13.4) Translocation

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Undifferentiated embryonal sarcoma of the liver is a highly malignant and aggressive tumor that occasionally arises within mesenchymal hamartoma of the liver (MHL), a benign tumor that typically occurs in young children. Undifferentiated embryonal sarcoma arising in MHL, as well as uncomplicated MHL, frequently harbor rearrangements of band 19q13.4, including the translocation t(11;19)(q13;q13.4). In this study we report the cloning and DNA sequence analysis of the translocation breakpoints in an undifferentiated embryonal sarcoma arising in MHL known to harbor t(11;19). In this case, the breakpoint at 11q13 occurred in the *MALAT1* gene, also known as ALPHA. *MALAT1* is rearranged in renal tumors harboring the t(6;11)(p21;q13) translocation, and noncoding *MALAT1* transcripts are overexpressed in a number of human carcinomas. The breakpoint at 19q13.4 occurs at a locus we refer to as *MHLB1*, for Mesenchymal Hamartoma of the Liver Breakpoint 1. Although the *MHLB1* locus does not contain a known gene, several human ESTs map to the region (a subset of which show homology to the nuclear RNA export factor (*NXF*) gene family), and the region is conserved between many mammalian species.

INTRODUCTION

Mesenchymal hamartoma of the liver (MHL) is a rare, benign, well-circumscribed tumor composed of an overgrowth of a mixture of loose mesenchyme, bile ducts, hepatocyte cords, and blood vessels (Ishak et al., 2001; Siddiqui and McKenna, 2006). The tumor typically occurs in young children, although cases in adults have also been described (Cook et al., 2002).

Possible etiologies for MHL include developmental anomalies, biliary obstruction, and regional ischemia (Okeda, 1976; Lennington et al., 1993; Ishak et al., 2001; Siddiqui and McKenna, 2006), but the recent demonstration of recurring chromosomal aberrations in MHL suggests that MHL is a neoplasm. In all reported cases with cytogenetic analysis, an aberration involving chromosomal region 19q13.4 has been present. Specifically, the t(11;19)(q13;q13.4) has been reported in three cases (Mascarello and Krous, 1992; Bove et al., 1998; Rakheja et al., 2004), whereas t(11;19)(q13;q13.3), t(15;19)(q15;q13.4), a complex rearrangement involving 11q2, 17p11 and 19q13.3, and an interstitial deletion del(19)(q13.1q13.4) have each been reported in single cases (Speleman et al., 1989; Murthi et al., 2003; Sharif et al., 2006; Talmon and Cohen, 2006).

Undifferentiated embryonal sarcoma (UES), previously referred to as malignant mesenchymoma (Stanley et al., 1973), is a highly malignant and aggressive tumor that shares several clinical and pathological features with MHL. Although the oncogenesis of UES remains uncertain (Stocker and Ishak, 1978), the reports of UES arising within MHL (de Chadarevian et al., 1994; Lauwers et al., 1997; Ramanujam et al., 1999; Begueret et al., 2001; O'Sullivan et al., 2001) suggest a link between the two tumors. In addition, karyotypic analysis of UES arising in MHL has demonstrated rearrangements of region 19q13.4, including t(11;19)(q11;q13.3–13.4) in one case (O'Sullivan et al., 2001), and add(19)(q13.4) in two cases

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(Sawyer et al., 1996; Lauwers et al., 1997), structural changes that are virtually identical to those reported for MHL as discussed earlier.

In this study we report the cloning and DNA sequence analysis of the translocation breakpoint in a case of UES arising in MHL known to harbor t(11;19)(q11;q13.3–13.4).

MATERIALS AND METHODS

Fluorescence In Situ Hybridization

Dual color fluorescence in situ hybridization (FISH) using probes labeled with rhodamine or FITC was performed on sections of formalin-fixed, paraffin-embedded tissue as described previously (Bridge et al., 2006) from a case of UES arising in MHL known to harbor the t(11;19)(q11;q13.3–13.4) translocation (O'Sullivan et al., 2001). Probes for FISH analysis consisted of BAC clones from chromosomes 11 and 19 identified via the UCSC Human Genome Browser (http://www.genome.ucsc.edu).

MHL BAC Library Construction

Approximately 0.5 g of MHL tissue, snap frozen at −70°C at the time of excision, was used to construct a tumor BAC library with a minimum of 5-fold coverage (BIO S & T, Montreal, Quebec, Canada). The library was screened by PCR using primers (Table 1) designed to target DNA stretches about 500 bp long in the region of the chromosome 19 breakpoint identified by FISH (Fig. 1). Positive tumor BAC clones were end sequenced to identify those spanning the translocation breakpoint. Full length sequence of tumor BAC clones was performed by the Genome Sequencing Center at Washington University School of Medicine.

Sequence Analysis of Breakpoint Regions From Tumor Tissue

Genomic DNA extracted from frozen tumor tissue was used as the template in nested PCR reactions using primers designed to amplify the breakpoint based on the sequence of the MHL BAC clones spanning the translocation breakpoint. For derivative chromosome 19, the initial primers were 5′-TGAATCAAATTCAGCAGCCACT-3′ and 5′-TCCAGGATTAATGTAGTGTAACA-3′, and the nested primers were 5′-TAAGGTCCGATCTGGCCTGT-3′ and 5′-TGAGATGGACATTGCCTCTTC-3′. For derivative chromosome 11, the initial primers were 5′-GCTTGAATGTCTTTTAGAGGGT-3′ (based on the sequence of the MHL BAC clones, which corresponds to the genomic sequence 5′-GCTTGAATGTCTCTTAGAGGGT-3′) and 5′-CAATTCTCCATTCTAGGCTATG-3′, and the nested primers were 5′-TTGAGTGGCAACCAGCCCG-3′ (based on the sequence of the MHL BAC clones, which corresponds to the genomic sequence 5′-CTGAGTCATAACCAGCCTG-3′) and 5′-TAAGACAGAGAAAGGCTATGCA-3′. The PCR products were cloned using the TA cloning kit (Invitrogen, Carlsbad, California), and then sequenced using the *Taq* dideoxy terminator cycle sequencing kit (Applied Biosystems, Foster City, California) and a fluorescent DNA sequencer (Model 373A, Applied Biosystems). Computer sequence analysis was performed using the UCSC Human BLAT Search (http://www.genome.ucsc.edu).

TABLE 1. PCR Primers Used for Screening the MHL BAC Library

Set 1	5′-ATTCGCAATTTTACTCAGGATGTAA-3′
	5′-ACACCCAGCCTTACGTGCCAT-3′
Set 2	5′-AGCACAGCCCAGTTTAGTCTGG-3′
	5′-GTACCATTCCAACAGGCAAAACC-3′
Set 3	5′-TCATGAGAACAGCAATGGATGTT-3′
	5′-GAGCAGCTGGGGTTACAGGCT-3′

RESULTS

Chromosome 19 Breakpoint Mapping

An initial round of dual color FISH, using BAC probes spaced every 2.5–5 Mb, narrowed the site of the breakpoint at 19q13.4 to a region ~3.2 Mb long (Fig. 1A). A second round of dual color FISH, using more closely spaced BAC probes, narrowed the site of the breakpoint to a region roughly 400 kb long (Fig. 1B).

Isolation of Tumor BACs Spanning the t(11;19) Breakpoint

Three facts constrained the next step in breakpoint mapping. First, no cell line was produced from the tumor; second, less than 1 g of frozen tumor tissue was available for study; and third, the breakpoint region identified by FISH mapping did not contain any loci known to be involved in tumorigenesis. Therefore, rather than to attempt to identify the breakpoint by 5′ or 3′ RACE, which would have exhausted our material, we opted to produce a BAC library from the frozen MHL tumor tissue. A PCR screen of the MHL library for target sequences spaced approximately every 75 kb in the breakpoint region (Fig. 1C) identified 12 clones that contained the region of interest. End sequence analysis of these clones identified

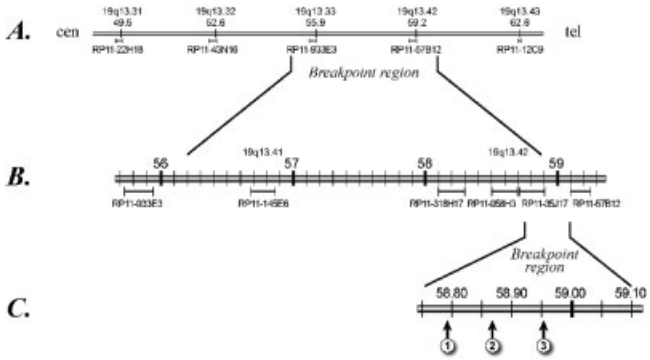

Figure 1. Schematic representation of the results of dual-color break-apart FISH mapping to identify the translocation breakpoint on chromosome 19. Panel A: Location of the first set of BAC probes used to map the translocation to a 3.2 Mb region. Panel B: Location of the second set of BAC probes used to refine the location of the translocation breakpoint to a region under 400 kb. Panel C: Vertical arrows indicate the location of the target regions used in the PCR-based screen of the MHL BAC library to identify clones potentially harboring tumor DNA spanning the t(11;19) breakpoint on chromosome 19. Numbers above the schematic chromosomes indicate the chromosomal band and the base position ($\times 10^6$) as assigned by http://www.genome.ucsc.edu.

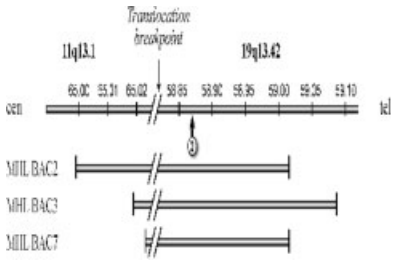

Figure 2. Schematic representation identifying the three clones from the MHL BAC library spanning the t(11;19) breakpoint on the derivative 11 (der11) chromosome. The position of the second target region used in the PCR-based screen of the MHL BAC library is indicated. Numbers above the der11 schematic chromosome indicate the chromosomal band and the base position ($\times 10^6$) as assigned by http://www.genome.ucsc.edu.

Figure 3. Sequence of the derivative chromosome 11 and 19 breakpoint regions. Panel A: Derivative chromosome 11. The underscore indicates the junction between the *MALAT1* gene on chromosome 11 and the *ACAT2* gene on chromosome 6, which is ambiguous due to identical sequences of the wild type chromosomes at this position. The sequence derived from *ACAT2* is in bold. The double underscore indicates nucleotides of uncertain origin at the junction between *ACAT2* sequence and chromosome 19. Panel B: Derivative chromosome 19. The underscore indicates the junction between chromosome 19 and the *MALAT1* gene of chromosome 11, which is ambiguous due to identical sequences of the wild type chromosomes at this position.

three that harbored an insert containing a breakpoint of the t(11;19) rearrangement (Fig. 2).

DNA Sequence Analysis of the t(11;19) Breakpoint

Sequence analysis of the insert in MHL BAC7, chosen because it had the shortest insert, was used to design primers to sequence the breakpoint region of both derivative chromosomes from genomic DNA isolated from frozen tumor tissue (Fig. 3).

The chromosome 11 breakpoint occurs in *MALAT1* (Ji et al., 2003; Lin et al., 2006), also known as ALPHA (James et al., 1994; Guru et al., 1997). The translocation also apparently involves chromosome 6 (despite the absence of structural changes in chromosome 6 in the tumor's reported karyotype) since the derivative chromosome 11 includes a 253 bp fragment with 100% homology to a region of intron 2 of the *ACAT2* gene (which encodes acetyl-CoA acetyltransferase 2, an enzyme involved in lipid metabolism) at 6q25.3 (Fig. 3A).

The chromosome 19 breakpoint occurs at a location that does not contain a known gene, although a number of human ESTs map to the region of the breakpoint (Fig. 4). Several of these ESTs (including D78693, BF994151, and BI051971) contain regions of sequence that are highly homologous to *NFX2* or *NFX3*, members of the nuclear RNA export factor (*NXF*) gene family (Izaurralde, 2001) (data not shown). Moreover, this region has high interspecies genomic conservation suggesting that it harbors a gene or has an important architectural function (Fig. 4).

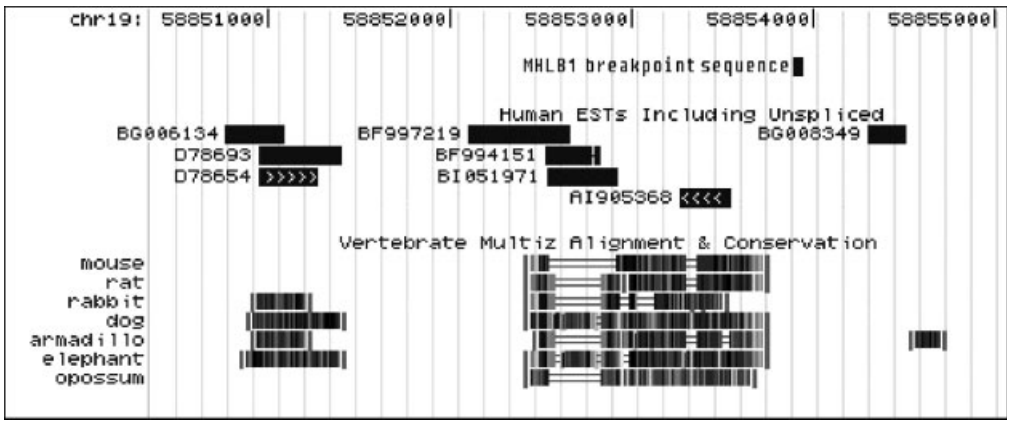

Figure 4. Expressed human ESTs and blocks of homologous sequence between mammalian species in the region of the chromosome 19 breakpoint. From UCSC Genome Browser (http://www.genome.ucsc.edu) on human March 2006 assembly (NCBI Build 36.1); numbers at the top of the diagram indicate the base position ($\times 10^6$).

DISCUSSION

In the present study we demonstrate that the breakpoint of the translocation t(11;19)(q11;q13.4) present in a UES arising in MHL involves the *MALAT1* gene on chromosome 11, and a locus on chromosome 19 that does not contain a known gene (for the purposes of this discussion, we will refer to this locus as *MHLB1* for Mesenchymal Hamartoma of the Liver Breakpoint 1).

Although the breakpoint region on chromosome 19 does not occur within a known gene, two features of the region suggest that the breakpoint occurs within a coding region. First, several human ESTs map to the region (Fig. 4), some of which show sequence homology to members of the *NXF* gene family (data not shown). Second, the breakpoint occurs within a region of blocks of homologous sequence between several mammalian species (Fig. 4), suggestive of a conserved coding region. It is noteworthy that the *MHLB1* locus occurs within a breakpoint cluster region for translocations characteristic of benign thyroid adenomas (Belge et al., 2001), indicating that the locus may have a role in the development of a number of neoplasms.

Rearrangements of *MALAT1* have been shown to be involved in the tumorgenesis of a subset of renal neoplasms harboring the t(6;11)(p21;q13), in which the gene is fused with *TFEB* upstream of *TFEB*'s start codon. In these renal neoplasms, overexpression of TFEB driven by the *MALAT1* promoter is thought to play a role in tumorigenesis (Davis et al., 2003), but it is of note that the site of the *MALAT1* translocation breakpoint in renal neoplasms is from 2.7 to 2.8 kb upstream of the site in the current case of UES arising in MHL. *MALAT1* thus appears to join the group of loci whose rearrangement is associated with different tumor types in different tissues, including as examples *FUS* in myxoid/round cell liposarcoma, acute myeloid leukemia, and low grade fibromyxoid sarcoma (Crozat et al., 1993; Kong et al., 1997; Storlazzi et al., 2003), *PLAG1* in pleomorphic adenoma of salivary glands and lipoblastoma (Kas et al., 1997; Hibbard et al., 2000), and *ALK* in inflammatory myofibroblastic tumor and anaplastic large cell lymphoma (Pfeifer, 2006).

The breakpoint we characterize is from a UES arising in MHL. Translocations or more complex rearrangements involving19q13.3–19q13.4 are a feature of the karyotype of virtually every case of MHL that has been subjected to conventional cytogentical analysis (Speleman et al., 1989; Ishak et al., 2001; Murthi et al., 2003; Rakheja et al., 2004; Sharif et al., 2006; Siddiqui and McKenna, 2006; Talmon and Cohen, 2006), and are also a recurring feature of UES arising in MHL (Sawyer et al., 1996; Lauwers et al., 1997; O'Sullivan et al., 2001). Similarly, translocations or other rearrangements involving 11q11–13 are present in most MHL (Speleman et al., 1989; Ishak et al., 2001; Murthi et al., 2003; Rakheja et al., 2004; Sharif et al., 2006; Siddiqui and McKenna, 2006) and a subset of UES arising in MHL (O'Sullivan et al., 2001). Thus, it is likely that the t(11;19) translocation is related to the development of MHL but that additional alterations of other loci are required for the tumorigenesis of UES, consistent with recent comparative genomic hybridization results that show UES is characterized by multiple amplifications and deletions (Sowery et al., 2001).

Although the mechanism of tumorigenesis of MHL (and UES) remains unknown, the sequence of the t(11;19) breakpoint suggests several scenarios.

By analogy with the renal neoplasms harboring *MALAT1* rearrangements, expression of *MALAT1-MHLB1* (or *MHLB1-MALAT1*) fusion transcripts may result in dysregulated production of peptides with growth promoting activities (Davis et al., 2003). Alternatively, given that *MALAT1* transcripts are known to be dysregulated in various malignancies (Ji et al., 2003; Lin et al., 2006), structural alterations of *MALAT1* as a result of the translocation may disrupt the function of the gene's noncoding RNA transcript. It is also possible that the *ACAT2* gene contributes to tumorigenesis; the fact that a rearrangement involving chromosome 6 was not apparent in the karyotype from the case we have studied may indicate that the gross structural aberrations characteristic of the karyotype of MHL and UES may not accurately reflect the diversity of the involved loci. In any event, analysis of the mechanism by which the t(11;19) promotes development of MHL (and potentially UES) in the case we report is complicated by the fact that no cell line was produced from the tumor, and that so little fresh tumor tissue was archived. Characterization of the mechanism of tumorigenesis will therefore require the use of hepatic cell lines transfected with the cloned breakpoint regions. Such studies are currently underway.

Finally, it is worth noting that the conventional approach to identification of the breakpoints of translocations characteristic of a specific tumor type generally involves low resolution mapping of the breakpoint region by FISH, followed by computer-based analysis of the breakpoint region to identify genes likely to participate in the translocation, followed by RACE of the candidate genes (and/or their transcripts) to demonstrate their involvement in the rearrangement. This conventional approach has been extremely successful at identifying translocations that create fusions of known genes. The method used in this study, in which the breakpoint is identified from a BAC library produced from tumor tissue, offers several advantages over the conventional approach. First, the technique provides the opportunity to genetically characterize a tumor even if only a small quantity of fresh tissue is available. Second, since the approach is not biased in favor of translocations that produce structural changes at known coding loci, the method makes it possible to clone breakpoints that are tumorigenic via novel or unanticipated mechanisms that are not conducive to RACE.

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