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The Mouse Homologue of the Tuberin Gene (TSC2) Maps to a Conserved Synteny Group between Mouse Chromosome 17 and Human 16p13.3

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Received September 19, 1994; revised October 15, 1994

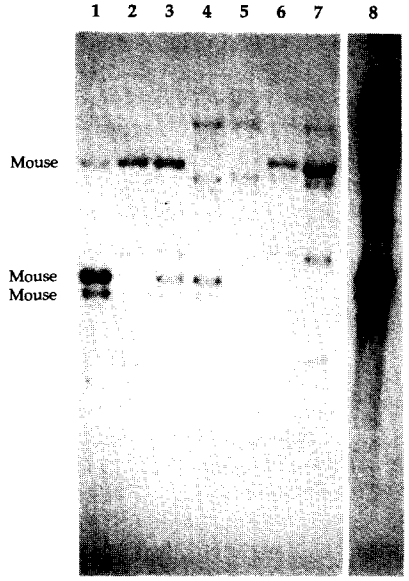

FIG. 1. Mapping of the mouse cDNA clone mTS-1. Genomic DNA was digested with *Hin*dIII. Lane **1,** mouse C3H liver DNA; lane **2,** hamster cell-line E 36 (1); lane **3,** somatic cell hybrid R 44, containing mouse chromosomes 17 and 18 on hamster background (7); lane **4,** somatic cell hybrid EJ167, containing mouse chromosomes 3 and 17 on human background (8); lane **5,** human GM1416B lymphoblastoid cell-line (ATCC); lane **6,** somatic cell hybrid RJ83.1FT, containing human chromosome 16 on hamster background (2); lane **7,** radiation hybrid 141.6, containing fragments of human chromosome 16 on hamster background (2); lane **8,** YAC M3, isolated using the D17Lon1 marker from the ICRF library (6). The 9- and 10-kb (faint) mouse bands seen in lanes **1** and **4,** respectively, correspond to a *Hin*dIII RFLV that is also observed between DBA/2 and C57BL/6 (in lane **3** the band is masked by a hamster band). The *Hin*dIII RFLV shows the same BXD strain distribution pattern as the *Taq*I RFLV, consistent with all bands hybridizing to the probe being on mouse chromosome 17 (data not shown).

The tuberous sclerosis gene (*TSC2*) on human chromosome 16p13.3 has recently been identified (11). Several markers from this region have previously been shown to be members of a conserved synteny group, in the mouse located on chromosome 17. The mouse region includes markers D17Lon1, D17Lon2, D17Lon3, and D17Lon4, which are linked to the α-globin pseudogene *Hba-ps4* on chromosome 17, while the corresponding human markers, NK12, NK92, sazD, and KM17, are linked to the functional α-globin locus near the tip of chromosome 16p (3). Since the human *TSC2* maps in close proximity to NK12 (2, 11), we wanted to investigate whether a mouse gene, homologous to *TSC2,* was present on mouse chromosome 17 and thus included in the conserved synteny group.

During the characterization of transcripts from the human *PKD1* region on human chromosome 16p13.3, we isolated three short clones encoding fragments of TSC2 from a human fetal brain cDNA library enriched for transcripts from the *PKD1* region (5). These *TSC2* clones were used as probes to screen a mouse teratocarcinoma (PCC4) cDNA library (Stratagene), at a final stringency of 0.3× SSC, 0.1% SDS at 65°C. One of the positive clones isolated, mTS-1, had a 2.8-kb insert. Two hundred bases from each end of the insert were sequenced, showing 88 and 83.5% identity to the human tuberin nucleotide sequence, with the 5′ end of the clone starting at position 2351 and the 3′ end ending at position 5265. The high degree of homology to the human tuberin sequence suggests that clone mTS-1 is indeed derived from the mouse homologue of *TSC2.*

A Southern blot panel of *Hin*dIII-digested DNA from hybrid cell lines was probed with the whole 2.8-kb insert from the clone mTS-1 (Fig. 1) and washed at a final stringency of 0.1× SSC, 0.1% SDS at 65°C. The hybridization pattern is consistent with the mouse gene mapping to chromosome 17 (Fig. 1, lanes 1, 3, and 4). Bands of the same sizes were also present in a *Hin*dIII digest of the mouse YAC M3, isolated with the probe D17Lon1, which maps to the conserved synteny group (Fig. 1, lane 8). Cross-hybridizing fragments were found in human and hamster DNA, with the human bands mapping to 16p13.3 (Fig. 1, lanes 4, 5, and 6).

To define the genetic position of the mouse tuberin homo-

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GENOMICS **25,** 339–340 (1995)
0888-7543/95 $6.00

logue on chromosome 17, we used the BXD recombinant inbred strain system (10). The mTS-1 clone was tested for restriction fragment length variants (RFLV) between the C57BL/6 and DBA/2, and a *Taq*I RFLV was chosen for further analysis. The *Taq*I-digested DNA gave three constant bands, 1.3, 2.4, and 4.7 kb; in addition, DBA/2 had two variant bands of 1.9 and 3.0 kb, while the C57BL/6 variant was a single 5.2-kb band. The strain distribution pattern of the mTS-1 *Taq*I polymorphism showed no difference compared to *Hba-ps4* and D17Lon1 in the 21 strains tested (data not shown). The BXD results give a distance between Hba-ps4 and mTS-1 of 0.0–8.4 cM for 99% confidence (9).

The D17Lon1 marker has been mapped proximal to *Hba-ps4* (4), while its human counterpart, NK12, has been localized proximal to the human α-globin (2). As the human *TSC2* maps close to NK12, the presence of mTS-1 on the same YAC as D17Lon1 thus implies a physical organization on mouse chromosome 17 similar to that on human 16p13.3. Our results confirm that the mouse homologue of *TSC2* is located within the conserved synteny group on mouse chromosome 17 and human chromosome 16p13.3, by physical and genetic linkage to D17Lon1 and by genetic linkage to *Hba-ps4*.

ACKNOWLEDGMENTS

This work was supported by the Imperial Cancer Research Fund and by a MRC-HGMP grant. We thank G. G. Germino, S. Somlo, M. C. Schneider, and S. T. Reeders for providing the cosmids used in the construction of the enriched cDNA library.

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