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The transcription factor DBP was originally discovered by virtue of its specific binding to the D-site of the albumin gene promoter, and the gene is expressed in most adult tissues although the protein has been found in significant quantities only in adult liver (Mueller et al. 1990). DBP and another member of the basic region/leucine zipper (bZIP) family of transcription factor proteins, the CCAAT/enhancer binding protein C/EBPa, cooperate to control the tissue-specific expression of the albumin gene (Mueller et al. 1990; Lichsteiner et al. 1987). However, DBP appears to be relatively specific in its choice of binding sites and activities, while C/EBPa has been implicated in the regulation of a much broader collection of genes (for example, Alberini et al. 1994). The two related factors also exert their influences on albumin expression during distinct phases of liver development, with DBP activity reaching its peak in adult tissues, and C/EBPa displaying significant activity during earlier periods of rat development (Mueller et al. 1990). Because of their roles in regulation of tissue-specific gene expression during development and their possible connection to specific developmental disorders, the chromosomal locations of bZIP transcription factor genes are of special interest.

The CEBPA gene has been localized to human Chromosome (Chr) 19q13.1 (Hendricks-Taylor et al. 1992) and to the proximal portion of mouse Chr 7 (Saunders and Seldin 1990). The gene encoding DBP has also recently been localized to human Chr 19q13 by fluorescent in situ hybridization (Khatib et al. 1994), presenting the possibility that the two liver-expressed bZIP transcription factor genes are closely linked in the genome and that their proximity might facilitate coordinated expression. However, a more accurate position for the human DBP gene has not been presented, and the homologous gene has not yet been mapped in mouse. We therefore sought to determine the position of the gene within the genetic map of mouse and the detailed physical map of human Chr 19.

To localize DBP more precisely in human Chr 19q, we hybridized a radiolabeled conserved mouse probe, KS-D, to high-density filter arrays of Chr 19-specific cosmids (Olsen et al. 1993). The cosmid clones present in this library have been organized into contigs with a restriction digest fingerprinting scheme (Carrano et al. 1989), ordered relative to one another, and assigned to specific regions of Chr 19 with high-resolution FISH mapping methods (Brandriff et al. 1994). The KS-D probe was derived as a *Eco*RV-*Rsa*I subclone from a genomic clone (KS-III) isolated from a phage library (constructed from DNA of the 129/Sv mouse strain in the Lambda Fix II vector; Stratagene) with the rat *Dbp* cDNA clone as probe (Mueller et al. 1990; L. Lopez-Molina and U. Schibler, unpublished). The 1.3-kb subclone contains the leucine zipper domain of the mouse *Dbp* gene in addition to approximately 1 kb of downstream sequences (L. Lopez-Molina and U. Schibler, unpublished).

Localization of the murine *Dbp* gene was accomplished through hybridization of a second mouse genomic clone, KS-VII, to Southern blots carrying *Bgl*II digests of 160 progeny of *Mus musculus* × *M. spretus* interspecific backcross [IB; (129/R1-*p* c^{ch}/*p* c^{ch} × *M. spretus*) × 129/R1-*p* c^{ch}/*p* c^{ch}; Johnson 1990]. The KS-VII probe was derived as the intact insert of a second phage genomic clone isolated from the Lambda Fix II library and was excised with *Not*I and recloned into the pBluescript II KS+/− phagemid vector before use. DNA from the phagemid clone was used directly as probe with total mouse DNA competition, as described (Stubbs et al. 1990). KS-VII detected *Bgl*II restriction fragments of 9.4 and 5.7 kb in 129/R1 and *M. spretus* DNA samples respectively. The segregation of these variant fragments was compared with those of the homologs of human 19q genes including *Kal1* (the murine version of KLK1), *Lhb*, and *Mag*. The *Lhb* cDNA clone detected a *Hin*cII fragment of 1.6 kb in 129/RI DNA, and 1.9 kb in *M. spretus* DNA. The *Mag* gene probe detected *Taq*I fragments of 6.0 kb and 5.2 kb in 129/RI and *M. spretus* DNA respectively. The *Kal1* gene was represented by a cDNA clone corresponding to the human KLK1 gene (Evans et al. 1988), which detected an *Eco*RI fragment of 2.8 kb in 129/RI DNA and a *M. spretus*-specific fragment of 3.2 kb. Mapping data for *Myod1*, whose homolog maps to human Chr 11p15 and which is located just beyond the distal border of the 19q homology region, were taken from a previous study with this same backcross (Johnson 1990) and are included as a point of reference. The distribution patterns for each of these mouse genes is summarized in Fig. 1.

KS-D sequences hybridized strongly to a cluster of seven overlapping positive human cosmids located in a contig that has been assigned to 19q13.3, in a position located approximately 400 kb proximal of cosmids containing the LHB gene, 2400 kb proximal of the contig containing KLK1 (Fig. 2). Both of these genes have been assigned to Chr 19q13.3-q13.4 in previous studies (Talmadge et al. 1983; Evans et al 1988). IB mapping studies allowed localization of the murine *Dbp* gene near the distal border of the region of homology between mouse Chr 7 and human Chr 19q, and tightly linked to the *Lhb* and *Kal1* genes in agreement with the human mapping studies (Fig. 2). Therefore, like CEBPA, DBP is located on human Chr 19q and mouse Chr 7.

However, our data also indicate that, in both species, the two related bZIP transcription factor genes are located a significant distance apart. Human CEBPA is located very near the centromere of human 19q, in band 19q13.1 (Hendricks-Taylor et al. 1992), approximately 14 Mb proximal of the DBP gene (Fig. 2; Ashworth et al., submitted). In the mouse, *Cebpa* has been mapped very near the myelin-associated glycoprotein gene *Mag* (Saunders and Seldin 1990); MAG and CEBPA are also close neighbors in human 19q13.1 (within 2 Mb, Fig. 1; Ashworth et al., submitted). In our

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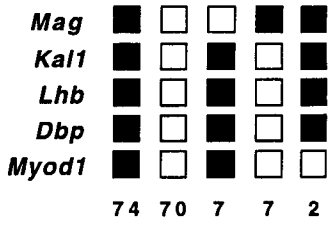

Fig. 1. Position of the mouse *Dbp* locus on mouse Chr 7. Segregation patterns of *Dbp* and neighboring genes in 160 backcross animals that were typed for all loci. Each column represents the chromosome inherited by backcross progeny from their 129/Rl × *Mus spretus* hybrid parent. Black boxes represent the presence of the 129/RI allele, and white boxes indicate that a *M. spretus* allele was detected at the particular locus. The number of offspring inheriting each type of chromosome is listed at the bottom of each column. The *Lhb* gene was represented by a cDNA clone obtained from the American Type Culture collection (ATCC, Rockville, Md.; Talmadge et al. 1983). *Kal1* was represented by a human cDNA clone, as described in the text. *Mag* was represented by a polymerase chain reaction (PCR) product generated with oligonucleotides (5′-tagcccctaccccaagaact-3′, 5′-acgttactgagcaggagg-3′) designed from the published human sequence (Sato et al. 1989) as primers for the sequence in a reaction containing 100 ng human genomic DNA, 0.2 Units Taq polymerase (Perkin-Elmer/Cetus) in buffer supplied by the manufacturer. The reaction was carried out in a GeneAmp 9600 thermocycler (Perkin-Elmer/Cetus) by use of 30 cycles with an annealing temperature of 57°C. Southern blotting, probe preparation, and hybridizations were carried out as previously described (Stubbs et al. 1990).

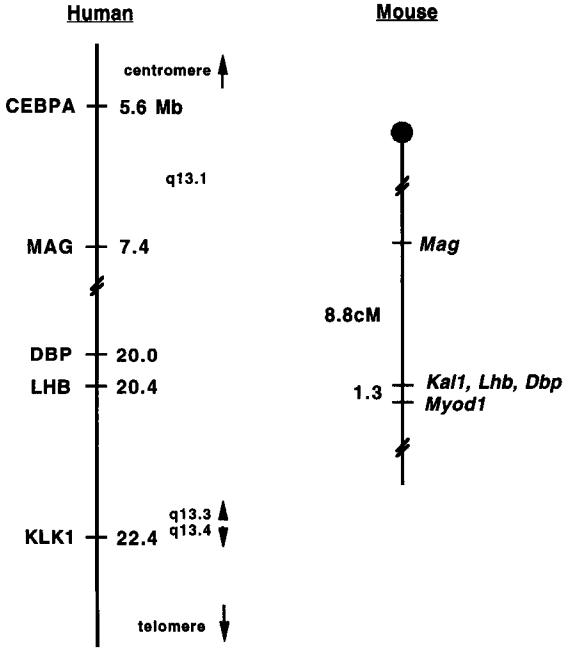

Fig. 2. Position of the DBP gene in human Chr 19q13.3 and mouse Chr 7. The position of DBP relative to neighboring human 19q13.3 genes, and to the CEPBA and MAG loci, was determined by physical mapping methods, as described in the text. Numbers directly adjacent to the map indicate the approximate distance of each gene from the 19q centromere, in Mb. Chromosome band positions are indicated at right: KLK1 is situated at the border of 19q13.3 and 19q13.4, as indicated by the arrowheads pointing toward each subband. Position of the *Mag, Dbp, Kal1,* and *Lhb* genes on mouse Chr 7 were calculated by standard methods (Silver 1985) from the segregation data obtained for each marker in the IB system, as summarized in Fig. 1. Map positions were calculated with the aid of Map Manager data analysis software (Manly 1993). Location of *Myod1,* as determined in this same IB system, is taken from the data of Johnson (1990). Numbers at the left of the mouse map indicate the genetic distance, in cM, estimated to separate adjacent sets of gene markers.

IB system, *Mag* is located approximately 8.8 cM (±2.2 cM) proximal of the position determined for *Dbp, Lhb,* and *Kal1* (Fig. 2), in fair agreement with distances between *Mag* and the clustered *Lhb* and *Kal1* genes determined in previous studies (11.4 cM was calculated as the distance between *Mag* and *Lhb* or *Kal1* by Saunders and Seldin 1990). The close linkage between *Mag* and *Cebpa* reported by these authors (0.9 cM), in combination with data presented here, would place *Cebpa* approximately 7 cM proximal of the mouse *Dbp* gene. The *Cebpa-Lhb* distance estimated by our data is thus smaller than that calculated in previously published reports (10.5 cM; Saunders and Seldin 1990), but the margins of error associated with both calculations put predictions of *Cebp-Dbp* distances derived from either study in reasonable agreement. Thus, it is clear that despite their genetic linkage, the two related and bZIP transcription factor genes, *Cebpa* and *Dbp,* are not clustered, and the coordination of expression and activities in developing liver cells cannot be attributed to factors relying on physical proximity in the mouse or human genomes.

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