Mammalian Genome 3: 184–185, 1992

Mammalian Genome

The gene coding for variant hepatic nuclear factor 1 (*Tcf-2*), maps between the *Edp-1* and *Erba* genes on mouse Chromosome 11

I. Jill Karolyi,[1] Jean-Louis Guénet,[2] Javier Rey-Campos,[3] and Sally A. Camper[1]

[1]Department of Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan 48109-0618, USA; [2]Unité de Génétique des Mammifères, Institut Pasteur; [3]Unité des Virus Oncogènes, Institut Pasteur, 25 rue du Docteur Roux, 75724 Paris, Cedex 15, France

Received November 7, 1991; accepted December 10, 1991

Variant Hepatic Nuclear Factor 1 (vHNF1), also called TCF2, HNF1β, or LFB3, is a nuclear protein that binds to proximal promoter sequences of α and β fibrinogen and albumin. The protein was first identified in dedifferentiated rat hepatoma cell lines (Baumhueter et al. 1988; Cereghini et al. 1988). The mRNA is found in significant levels in adult rat and mouse kidney and in low levels in liver, intestine, and lung (Rey-Campos et al. 1991; De Simone et al. 1991; Mendel et al. 1991). The cDNA corresponding to the rat mRNA has been isolated and sequenced from the dedifferentiated hepatoma H5 cell line (Rey-Campos et al. 1991). The human and mouse cDNAs have also been isolated and share approximately 93% sequence homology with the rat cDNA (Bach et al. 1991; De Simone et al. 1991; Mendel et al. 1991). The gene codes for a homeoprotein homologous to Hepatic Nuclear Factor 1 (HNF1) or LFB1 in regions important for DNA binding and dimerization while the sequence is highly divergent in the transactivation domain. Both HNF1 and vHNF1 act as transcriptional activators of the albumin promoter in transient co-transfection experiments, and these proteins form heterodimers (Rey-Campos et al. 1991). Though HNF1 and vHNF1 are two closely related homeoproteins, they are localized on different chromosomes. HNF1 has been previously mapped to mouse Chr 12 and human Chr 5 (Bach et al. 1990).

Transcription factor 2 (*Tcf-2*) has been assigned to mouse Chr 11 and human Chr 17 by analysis of somatic cell hybrids (Milatovich et al. 1991). In situ hybridization has localized the gene to human Chr 17q11.2-q21.1 and mouse Chr 11B4-D (Bach et al. 1991). We report chromosomal location of mouse *Tcf-2* relative to other previously mapped Chr 11 loci using an intersubspecific mouse backcross. This (DF/B-*df*/*df* × CASA/Rk)F_1 × DF/B-*df*/*df* backcross has been typed for 12 loci on Chr 11 (Buckwalter et al. 1991). Southern blotting and probe labeling was done by standard methods.

An informative *CASA/Rk Bam*HI polymorphism was detected with the *Tcf-2* probe (Fig. 1). A DF/B-*df*/*df* specific fragment is located at 7.5 kb and a *CASA/Rk* specific fragment at 6.8 kb. The results of typing 86 animals for endothelial cell-derived protein (*Edp-1;* Wolf et al. 1992; Buckwalter et al. 1991), *Tcf-2*, and Avian erythroblastosis virus oncogene A (*Erba*) (Lazar et al. 1988; Buckwalter et al. 1991) are given in Table 1. Five recombinants were found between *Edp-1* and *Tcf-2*, placing *Tcf-2* 5.8 ± 2.5 cM (centimorgans ± standard deviation) distal to *Edp-1* on Chr 11. Fourteen recombinants were found between *Tcf-2* and *Erba*, placing *Tcf-2* 16.3 ± 4.0 cM proximal to *Erba* on this chromosome. This mapping generates the following gene order: *Edp-1*–5.8 cM–*Tcf-2*–16.3 cM–*Erba*.

This localization corrects the preliminary mapping of *Tcf-2*, also known as *D11Pas3*, in an interspecific backcross with *Mus spretus* performed in the laboratory of J.-L. Guénet (Buchberg et al. 1991). Further analysis of those data places *Tcf-2* between *Csfgm* and *Gfap*, confirming our mapping of *Tcf-2*. In 22 progeny, there was one recombinant between *Csfgm* and *Tcf-2*, and there were four between *Tcf-2* and *Gfap*.

Homeobox-2, (*Hox-2*) a cluster of homeotic genes on Chr 11, has been mapped 0.7 ± 0.7 cM proximal to *Erba* (Buchberg et al. 1989). The 95% confidence limits for the *Erba–Hox-2* and *Erba–Tcf-2* distances are not overlapping. Thus, *Tcf-2* is localized outside this cluster of other homeotic genes. This was further confirmed by detection of four recombinants out of 22 progeny typed for both *Tcf-2* and *Hox-2* in the interspecific backcross with *M. spretus* mentioned above.

This multipoint molecular genetic localization of *Tcf-2* is consistent with the in situ hybridization of *Tcf-2* to mouse 11B4-D. Our localization of *Tcf-2* corresponds to 11B4 (Buchberg et al. 1991). Our mapping is also consistent with the in situ localization of the human gene to 17q11.2-21.1 because the genes that we

Offprint requests to: S.A. Camper

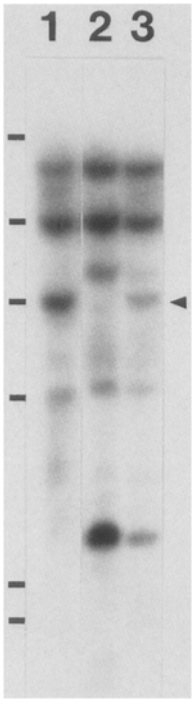

Fig. 1. Southern blot identification of a unique *M. castaneus* (*CASA/Rk*) RFLP in *Tcf-2*. An **arrowhead** signifies the 6.8-kb fragment present in genomic DNA from *CASA/Rk* **(lane 1)** and from an animal heterozygous for DF/B-*df/df* and *CASA/Rk* **(lane 3),** but absent in an animal homozygous for DF/B-*df/df* at this locus **(lane 2).** Digests were performed with the restriction endonuclease *Bam*HI. Molecular size standard is λ DNA-*Hin*dIII fragments.

mapped proximal (*Edp-1*) and distal (*Erba*) to *Tcf-2* also map to human Chr 17. *Edp-1* maps to human 17q22-23 (Wolf et al. 1992), and *Erba* maps to human 17q11.2-21 (Buchberg et al. 1991). The localization of *Tcf-2* near *Edp-1* is consistent with the synteny conservation and lack of linkage conservation observed between mouse Chr 11 and human Chr 17 (Buchberg et al. 1989).

Table 1. Segregation of three loci on Chr 11 among 86 backcross offspring from the cross (DF/B-*df/df* × *CASA/Rk*)F_1 × DF/B-*df/df*. The symbols D and C represent DF/B-*df/df*-derived and *CASA/Rk*-derived alleles, respectively.

	Loci inherited from F_1 parent			Number of progeny
	Edp-1	*Tcf-2*	*Erba*	
Nonrecombinants	D	D	D	34
	C	C	C	33
Single recombinants	D ×	C	C	4
	C	D	D	1
	D	D ×	C	5
	C	C	D	9

Acknowledgments. We thank Marion S. Buckwalter for providing us with *Bam*HI filters of the backcross progeny and for helpful comments regarding the manuscript. This research was supported by a National Science Foundation grant DCB-9004449.

References

Bach, I., Galcheva-Gargova, Z., Mattei, M.G., Simon-Chazottes, D., Guénet J.-L., Cereghini, S., and Yaniv, M.: Cloning of human hepatic nuclear factor 1 (HNF1) and chromosomal localization of its gene in man and mouse. *Genomics 8:* 155–164, 1990.

Bach, I., Mattei, M.-G., Cereghini, S., and Yaniv, M.: Two members of an HNF1 homeoprotein family are expressed in human liver. *Nucleic Acids Res 19:* 3553–3559, 1991.

Baumhueter, S., Courtois, G., and Crabtree, G.R.: A variant nuclear protein in dedifferentiated hepatoma cells binds to the same functional sequences in the β fibrinogen gene promoter as HNF-1. *EMBO J 7:* 2485–2493, 1988.

Buchberg, A.M., Brownell, E., Nagata, S., Jenkins, N.S., and Copeland, N.G.: A comprehensive genetic map of murine Chromosome 11 reveals extensive conservation between mouse and human. *Genomics 122:* 153–161, 1989.

Buchberg, A.M., Moskow, J.J., Buckwalter, M.S., and Camper, S.A.: Mouse Chromosome 11. *Mammalian Genome 1 (Suppl):* S158–S191, 1991.

Buckwalter, M.S., Katz, R.W., and Camper, S.A.: Localization of the panhypopituitary dwarf mutation (*df*) on mouse Chromosome 11 in an intersubspecific backcross. *Genomics 10:* 515–525, 1991.

Cereghini, S., Blumenfeld, M., and Yaniv, M.: A liver-specific factor essential for albumin transcription differs between differentiated and dedifferentiated rat hepatoma cells. *Genes Dev 2:* 957–974, 1988.

De Simone, V., De Magistris, L., Lazzaro, D., Gerstner, Y., Monaci, P., Nicosia, A., and Cortese, R.: LFB3, a hererodimerforming homeoprotein of the LFB1 family, is expressed in specialized epithelia. *EMBO J 10:* 1435–1443, 1991.

Lazar, M.A., Hodin, R.A., Darling, D.S., and Chin, W.W.: Identification of a rat c-erbAα-related protein which binds deoxyribonucleic acid but does not bind thyroid hormone. *Mol Endocrinol 2:* 893–901, 1988.

Mendel, D.B., Hansen, L.P., Graves, M.K., Conley, P.B., and Crabtree, G.R.: HNF-1α and HNF-1β (vHNF-1) share dimerization and homeo domains, but not activation domains, and form heterodimers in vitro. *Genes Dev 5:* 1042–1056, 1991.

Milatovich, A., Mendel, D.B., Graves, M.K., Crabtree, G.R., and Franke, U.: TCF2, the gene for hepatocyte nuclear factor-1 β, confirmed on human chromosome 17 and mapped to mouse chromosome 11 by Southern blot analysis of somatic cell hybrids. *Hum Gene Mapping 11:* 168, 1991.

Rey-Campos, J., Chouard, T., Yaniv, M., and Cereghini, S.: vHNF1 is a homeoprotein that activates transcription and forms heterodimers with HNF1. *EMBO J 10:* 1445–1457, 1991.

Wolf, F.W., Marks, R.M., Sarma, V., Byers, M.G., Katz, R.W., Shows, T.B., and Dixit, V.M.: Characterization of a novel tumor necrosis factor-α inducible endothelial primary response gene. *J Biol Chem 267:* 1317–1326, 1992.