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Chromosomal Localization of Three Pulmonary Surfactant Protein Genes in the Mouse

KAREN J. MOORE, MELANIE A. D'AMORE-BRUNO,* THOMAS R. KORFHAGEN,* STEPHAN W. GLASSER,* JEFFREY A. WHITSETT,* NANCY A. JENKINS, AND NEAL G. COPELAND[1]

*Mammalian Genetics Laboratory, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, P.O. Box B, Building 539, Frederick, Maryland 21702; and *Division of Pulmonary Biology, Children's Hospital Medical Center, College of Medicine, 231 Bethesda Avenue, Cincinnati, Ohio 45267-0541*

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Pulmonary surfactant, a protein–phospholipid mixture, maintains surface tension at the lung epithelium/air interface preventing alveolar collapse during respiration. For mammals appropriate developmental production of surfactant is necessary for adaptation to the air breathing environment. Deficiency of pulmonary surfactant results in respiratory distress syndrome (RDS), a leading cause of death in premature infants. Recently, three lung-specific pulmonary surfactant proteins designated SP-A, SP-B, and SP-C have been described. Cloned sequences for the genes that encode each of these proteins have been partially characterized in humans and other species. Analysis of interspecific backcross mice has allowed us to map the chromosomal locations of these three genes in the mouse. The gene encoding SP-A (*Sftp-1*) and the gene encoding SP-C (*Sftp-2*) both map to mouse chromosome 14, although at separate locations, while the gene encoding SP-B (*Sftp-3*) maps to chromosome 6. The mouse map locations determined in this study for the *Sftp* genes are consistent with the locations of these genes on the human genetic map and the syntenic relationships between the human and the mouse genomes.

INTRODUCTION

Pulmonary surfactant, a complex mixture of phospholipid and proteins (King, 1982), lines the lung alveolar epithelium, maintaining the structural integrity of the mammalian airway during respiration. Appropriate developmental production of pulmonary surfactant is required for successful adaptation from the *in utero* environment to the air-breathing environment. Lack of surfactant results in alveolar collapse and leads to respiratory distress syndrome (Avery and Mead, 1959), a major cause of morbidity and mortality in premature human infants.

The Type II epithelial cell, which composes 5% of the alveolar epithelium, is the major site of surfactant production (Dobbs *et al.*, 1982). Type II cells package surfactant within lamellar bodies that are secreted into the alveolar space where the surfactant is released (reviewed in Weaver and Whitsett, 1991). The two major phospholipid components of surfactant are dipalmitoyl phosphatidylcholine and phosphatidyglycerol (King, 1982). To date, three lung-specific surfactant-associated proteins, SP-A, SP-B, and SP-C, have been identified and partially characterized from lung lavage material (reviewed in Weaver and Whitsett, 1991). The hydrophobic surfactant proteins, SP-B and SP-C, appear to enhance the surfactant-like properties of the phospholipids (reviewed in Weaver and Whitsett, 1991) and appear to be essential components of biophysically active surfactant (Whitsett *et al.*, 1986). While SP-A's function has not been precisely defined, it does enhance the biophysical activity of surfactant phospholipids in the presence of SP-B and SP-C (Hawgood *et al.*, 1987) and aggregates phospholipids in a calcium-dependent manner (Hawgood *et al.*, 1985). SP-A and SP-B both appear to play a role in the formation of tubular myelin-like structures *in vitro* (Suzuki *et al.*, 1989).

The human *SFTP1* locus, which codes for the SP-A protein, maps to human chromosome 10q21–q24 (Bruns *et al.*, 1987; Fisher *et al.*, 1987) and consists of at least one functional gene and one pseudogene (Korfhagen *et al.*, 1991). Other species, including rat (Fisher *et al.*, 1988a), rabbit (Boggaram *et al.*, 1988) and mouse (Korfhagen *et al.*, 1990), each possess a single *SFTP1* gene based on Southern blot hybridization studies. The single *SFTP-2* locus, which encodes the SP-C protein, maps to human chromosome 8p (Glasser *et al.*, 1988b; Fisher *et al.*, 1988b). Recently, the 3.2-kb murine *Sftp-2* gene that encodes a single mRNA of 0.8 kb has been isolated and characterized (Glasser *et al.*, 1990). In humans, the *SFTP3* locus, which codes for the SP-B protein, maps to chromosome 2 (Pilot-Matias *et al.*, 1989) and consists of a single gene with no closely related pseudogenes.

Although the genetic map location for each of these *SFTP* genes is known in human they had not been previously mapped in the mouse. The genetic mapping of

[1] To whom correspondence should be addressed.

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these murine genes will address the question of whether any known mutation is a candidate for an altered *Sftp* gene and will also provide additional information about synteny between the human and the mouse genetic maps.

To define the chromosomal locations of the murine pulmonary surfactant protein genes, *Sftp-1, Sftp-2,* and *Sftp-3,* we have utilized an interspecific backcross analysis (reviewed in Avner *et al.,* 1988; Guenet, 1989). The interspecific backcross (IB) used in this analysis involved crosses of C57BL/6J females to *Mus spretus* males, followed by backcrossing hybrid F_1 females to C57BL/6J males. To date more than 700 loci have been placed on this IB map at an average resolution of less than 2.5 cM (Copeland and Jenkins, 1991), thus allowing the placement of any new locus on the linkage map.

The comparison of the segregation patterns seen for RFLPs for each of *Sftp-1, Sftp-2,* and *Sftp-3* to previously mapped loci has allowed these loci to be mapped on the mouse IB genetic map. *Sftp-1* and *Sftp-2* both map to mouse chromosome 14, although they are not closely linked, while *Sftp-3* maps to mouse chromosome 6. All three genes mapped in regions of conserved linkage homology between humans and mice.

MATERIALS AND METHODS

Mice. Interspecific backcross progeny were generated by mating (C57BL/6J × *M. spretus*)F_1 females and C57BL/6J males as previously described (Buchberg *et al.,* 1988, 1989). The backcross was performed at the NCI-Frederick Cancer Research and Development Center. The *M. spretus* mice were at F_7, F_9, F_{10}, F_{12}, F_{15}, or F_{17} generation of inbreeding when backcrosses were performed and were a gift from E. M. Eicher (The Jackson Laboratory, Bar Harbor, ME). Various subsets of the 205 N_2 progeny were used for mapping the *Sftp* genes.

Probes. The pulmonary surfactant SP-A (*Sftp-1*) probe (designated pmSPA1.2H) is a 1.2-kb murine genomic *Hin*dIII fragment isolated from a DBA/2J library (Korfhagen, unpublished data). This genomic fragment was cloned into pUC19 and includes 100 bp of intron 5 and all of exon 6 of the mouse *Sftp-1* gene. Two probes were used for mapping the pulmonary surfactant apoprotein-3 (*Sftp-3*) gene: a human 2.0-kb cDNA (designated p20c) cloned into pKC4, which contains 13 bp of 5′ untranslated and the entire coding and 3′ untranslated region of human *Sftp-3* (Glasser *et al.,* 1987); and a 1.5-kb murine cDNA (designated p16.2e) in pBluescript, which contains coding sequence beginning at the second codon and the entire 3′ untranslated sequence (D'Amore-Bruno, unpublished data). The pulmonary surfactant SP-C (*Sftp-2*) probe (designated p2.1) is a 0.85-kb human cDNA cloned into pUC. It extends from the coding sequence through the polyadenylation site (Glasser *et al.,* 1988b). All probes were labeled with [^{32}P]αdCTP using a nick-translation kit from Boehringer Mannheim as described by the manufacturer.

Southern blot analysis. Genomic DNA preparation, restriction enzyme analysis, agarose gel electrophoresis, and Southern blot transfer were performed as previously described (Jenkins *et al.,* 1982) with the following exceptions. The restricted DNA was electrophoresed through 0.8% agarose gels and transferred to Zetabind (Cuno, Inc.). After hybridization the blots were washed twice with 1× SSC, 0.1% SDS for 30 min at 65°C, and then with 0.2× SSCP, 0.1% SDS for 30 min at 65°C. The blots hybridized with the human *Sftp-3* cDNA probe were washed at a final stringency of 0.5× SSCP, 0.1% SDS.

Statistical analysis. The computer program SPRETUS MADNESS was used to determine gene order by minimizing the number of double recombinants required to explain the allele distribution patterns ("pedigree analysis," Avner *et al.,* 1988). Calculation of map distances was performed as described (Green, 1981).

RESULTS AND DISCUSSION

The chromosomal locations of murine *Sftp-1, Sftp-2,* and *Sftp-3* were determined by examining the distribution of *M. spretus*-specific RFLPs resulting from Southern blot analysis of DNAs from a (C57BL/6J × *M. spretus*) × C57BL/6J interspecific backcross. The backcross progeny were either homozygous for the C57BL/6J allele or heterozygous for the C57BL/6J and *M. spretus* alleles. No abnormal segregation patterns were observed. The various RFLPs used for mapping are listed in Table 1.

The *Sftp-1* locus, which codes for the SP-A pulmonary surfactant protein, mapped to the proximal portion of murine chromosome 14 (Fig. 1). In addition to the 76 N_2 progeny shown in Fig. 1, N_2 progeny that were typed for subsets of the loci are included in the determination of recombination distance. *Sftp-1* is located between the previously mapped loci plasminogen activator urokinase (*Plau*) (Ceci *et al.,* 1990) and bone morphogenetic protein-2b1 (*Bmp-2b1*) (Dickinson *et al.,* 1990). The ratios of the total number of mice carrying recombinant chromosomes to the total number of mice analyzed for each pair of loci and the most likely gene order are: centromere–*Plau*–(19/183)–*Sftp-1*–(3/91)–*Bmp-2b1.* The recombination frequencies, expressed as genetic distance in centimorgans ± the standard error, between each pair of loci are *Plau*–10.4 ± 2.3 cM–*Sftp-1*–3.30 ± 1.9 cM–*Bmp-2b1.*

The *Sftp-2* locus, which encodes the pulmonary surfactant protein SP-C, also maps to mouse chromosome 14 (Fig. 1), although approximately 20 cM distal to *Sftp-1.* In addition to the 136 N_2 progeny shown in the haplotype diagram of Fig. 1, N_2 progeny that were typed for a subset of the loci are included in the determination of recombination distance. There were no recombinants between *Sftp-2* and bone morphogenic protein-1 (*Bmp-1*) in 141 mice typed for both. At the upper 95% confidence limit these two loci are within 2.1 cM. The proximal marker used to place *Sftp-2* on the chromosome 14 linkage map was cytotoxic T lymphocyte-associated protein-1 (*Ctla-1*), which was previously mapped to chromosome 14 (Ceci *et al.,* 1990). The distal marker was hairless (*hr*), which had also been previously mapped to chromosome 14 (Ceci *et al.,* 1990). The ratios of the total number of mice carrying recombinant chromosomes to the total number of mice analyzed for each pair of loci and the most likely gene order are: centromere–Ctla-1–(18/160)–*Bmp-1*–(0/141)–*Sftp-2*–(1/170)–*hr.* The recombination frequencies, expressed as genetic distance in centimorgans ± the standard error, between each pair of loci are *Ctla-1*–11.3 ± 2.5 cM–*Bmp-1, Sftp-2*–0.6 ± 0.6 cM–*hr.*

Sftp-3, the locus that encodes the pulmonary surfactant protein SP-B, mapped to the proximal portion of

TABLE 1

Loci Abbreviations, Loci Names, Probes, and RFLPs Used for IB Mapping

Locus	Gene name	Probe	Enzyme	Restriction fragment sizes in kb	
				C57BL/6J	*M. spretus*
Sftp-1	Pulmonary surfactant apoprotein-1	Mouse genomic (pmSPA1.2H)	*Pvu*II	3.6	10.5
Sftp-2	Pulmonary surfactant apoprotein-2	Human cDNA (p2.1)	*Pst*I	5.4	7.2
Sftp-3	Pulmonary surfactant apoprotein-3	Mouse cDNA (p16.2e)	*Taq*I[a]	4.1	3.2
			*Pvu*II[a]	4.0, 3.3 2.4, 2.0	3.0
		Human cDNA (p20c)	*Pvu*II	3.3	3.0

[a] The same locus was followed using two different enzymes. Some animals were typed from *Taq*I-digested DNAs and some from *Pvu*II-digested DNAs.

murine chromosome 6 (Fig. 2). Other loci in this region of chromosome 6 that were used to define the map position of *Sftp-3* are homeobox-1.3 (*Hox-1.3*) (Siracusa *et al.*, 1991), Casitas B-lineage lymphoma oncogene-1 (*Cbl-1*) (Regnier *et al.*, 1989, Siracusa *et al.*, 1991), immunoglobulin kappa chain (*Igk*) (Regnier *et al.*, 1989, deLapeyriere *et al.*, 1990; Siracusa *et al.*, 1991), actin like protein-4 (*Act-4*) (Justice *et al.*, 1990), and *ras*-related fibrosarcoma oncogene (*Raf-1*) (deLapeyriere *et al.*, 1990, Goodwin *et al.*, 1991). In addition to the 55 N_2 progeny represented in the haplotype data of Fig. 2, further N_2 progeny were typed for a subset of the loci to more accurately determine recombination distances. The ratios of the total number of mice carrying recombinant chromosomes to the total number of mice analyzed for each pair of loci and the gene order are: centromere–*Hox-1.3*–(4/159)–*Cbl-1*–(3/156)–*Igk*–(1/152)–*Sftp-3*–(2/77)–*Act-4*–(17/94)–*Raf-1*. The recombination distances ± the standard error between each pair of loci are *Hox-1.3*–2.5 ± 1.2 cM–*Cbl-1*–1.9 ± 1.1 cM–*Igk*–0.7 ± 0.7 cM–*Sftp-3*–2.6 ± 1.8 cM–*Act-4*–18.1 ± 4.0 cM–*Raf-1*.

Each of the *Sftp* genes mapped to regions of conserved linkage homology between mice and humans. For example, *Sftp-1* mapped to mouse chromosome 14 in a region of human chromosome 10 homology. Mouse chromosome 14 has two regions of synteny with human chromosome 10 [A. L. Hillyard, D. P. Doolittle, M. T. Davisson, and T. H. Roderick, a computerized database maintained at The Jackson Laboratory, Bar Harbor, Maine (GBASE)]. One region of synteny lies in the proximal region of mouse chromosome 14 and includes *Sftp-1*, retinol binding protein-3 (*Rbp-3*) (human 10q11) (Liou *et al.*, 1987; Farrer *et al.*, 1988; Nakamura *et al.*, 1988; Mathew *et al.*, 1989; Carson and Simpson, 1989), *Plau* (human 10q24–qter) (Tripputi *et al.*, 1985; Ceci *et al.*, 1990), and adenosine kinase (*Adk*) (human 10q11–q24) (Francke and Thompson, 1979; Samuelson and Farber, 1985). The second region of synteny, defined by glutamate dehydrogenase (*Glud*), which maps to human chromosome 10q23–q24 (Hanauer *et al.*, 1985, 1987), maps near the middle of mouse chromosome 14.

In humans there is at least one *SFTP1* pseudogene (Korfhagen *et al.*, 1991) that also maps to human chromosome 10, whereas in the mouse there is no current evidence for any pseudogenes. The existence of a *SFTP1* pseudogene in humans but not in the mouse indicates that the appearance of the *SFTP1* pseudogene occurred subsequent to the divergence of mouse and man.

In humans *SFTP2* maps to chromosome 8p (Glasser *et al.*, 1988b; Fisher *et al.*, 1988b). The localization of *Sftp-2* to mouse chromosome 14 near *Bmp-1*, which also maps to human chromosome 8, (Tabas *et al.*, 1991) defines a new region of synteny between mouse and human. Examination of the data available from GBASE for mouse chromosome 14 reveals that retinoblastoma-1 (*Rb-1*) (human chromosome 13q14) (Ward *et al.*, 1984; Friend *et al.*, 1986; Lee *et al.*, 1987; Bowcock *et al.*, 1988) maps to the same chromosomal location as *hr* (Hsieh *et al.*, 1989; Bernard *et al.*, 1989; Stone *et al.*, 1989). As *hr* is only 0.6 cM distal from *Sftp-2*, the breakpoint of the regions of homology between human chromosomes 8 and 13 is defined within this narrow interval. The proximal extent of the human chromosome 8 synteny to mouse chromosome 14 is defined by the localization of glutamate dehydrogenase (*Glud*), which has been placed 2 cM proximal to *Bmp-1* (GBASE).

Finally, *Sftp-3* maps to mouse chromosome 6 within a region syntenic with human chromosome 2. This is consistent with the placement of *SFTP3* on human chromosome 2 (Pilot-Matias *et al.*, 1989). Other human chromosome 2 loci that map in this region include immunoglobin kappa chain complex (*Igk*) (human 2p12) (Malcolm *et al.*, 1982; McBride *et al.*, 1982; Lorenz *et al.*, 1987), which is 0.7 cM proximal to *Sftp-3;* two lymphocyte antigens, *Ly-2* and *Ly-3* (human 2p11 and 2, respectively); and fatty acid binding protein-1, liver (*Fabp1*) (human 2p11). Figure 2 also shows the approximate position of *Raf-1* (*ras*-related fibrosarcoma oncogene) (de-

Lapeyriere *et al.*, 1990; Goodwin *et al.*, 1991). *Raf-1* maps to human chromosome 3p25 (Bonner *et al.*, 1984; Teyssier *et al.*, 1986; Gerber *et al.*, 1988) and delineates the most distal location for the human chromosome 2 synteny. Likewise the mapping of *Hox-1.3* to human 7p21–p14 delineates the current proximal extent of the human chromosome 2 synteny.

In summary, this work assigns the chromosomal locations of three pulmonary surfactant genes in the mouse. Two of the genes, *Sftp-1*, which encodes pulmonary surfactant protein A, and *Sftp-2*, which encodes pulmonary surfactant protein C, map to separate locations on mouse chromosome 14. The *Sftp-3* gene, which encodes pulmonary surfactant protein B, maps to mouse chromosome 6. The map locations of *Sftp-1* and *Sftp-3* are consistent with previously reported syntenic regions between the human and mouse genomes, while the mapping of *Sftp-2* defines a new syntenic region. None of the locations are close to any mutation in the mouse that can be associated with a defect in a lung-specific gene.

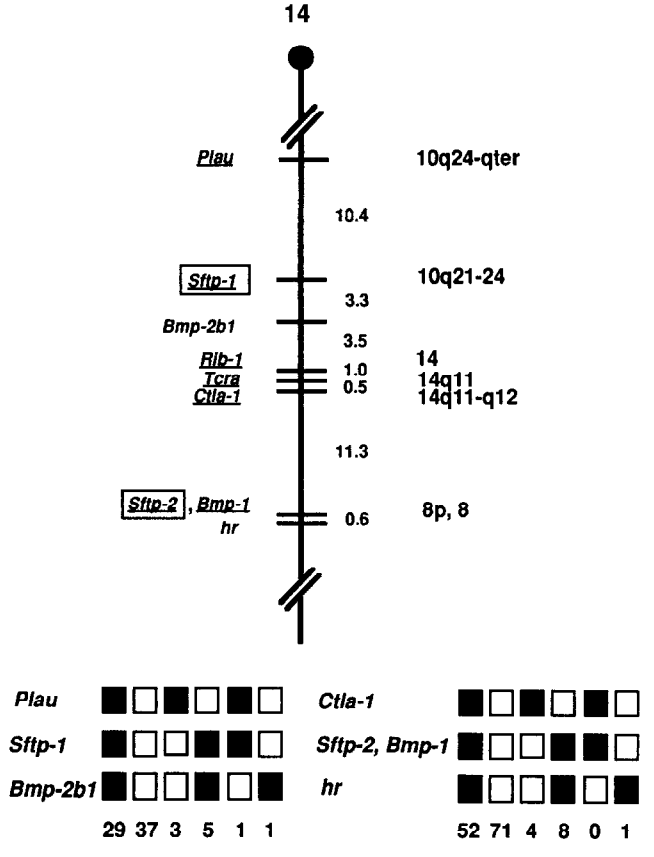

FIG. 1. The chromosomal locations and the haplotype data for the *Sftp-1* and *Sftp-2* genes on mouse chromosome 14. The haplotype block diagrams indicate the segregation of loci in (C57BL/6J × *Mus spretus*) × C57BL/6J interspecific backcross progeny. Genes used to map the *Sftp*'s in this analysis are shown on the left. Each column represents the chromosomes identified in the N_2 progeny that were inherited from the (C57BL/6J × *M. spretus*)F_1 parent. The shaded boxes represent the presence of a C57BL/6J allele, and the white boxes represent the presence of a *M. spretus* allele. The number of offspring inheriting each type of chromosome is shown at the bottom. Only those mice that could be typed for all the loci indicated are represented in the haplotype data. These data give gene order. The genetic distances, in centimorgans, are calculated from all available data, as presented under Results and Discussion and are shown to the right on the partial map of chromosome 14. Some additional genes, pancreatic ribonuclease-1 (*Rib-1*), T cell receptor α (*Tcra*), cytotoxic T lymphocyte-associated protein-1 (*Ctla-1*), and distances, which were determined by Ceci *et al.* (1990), are also shown. Boxed loci are the *Sftp* genes being mapped in this study. Mouse genes that have been mapped in humans are underlined. Locations of these genes on human chromosomes are shown at the far right.

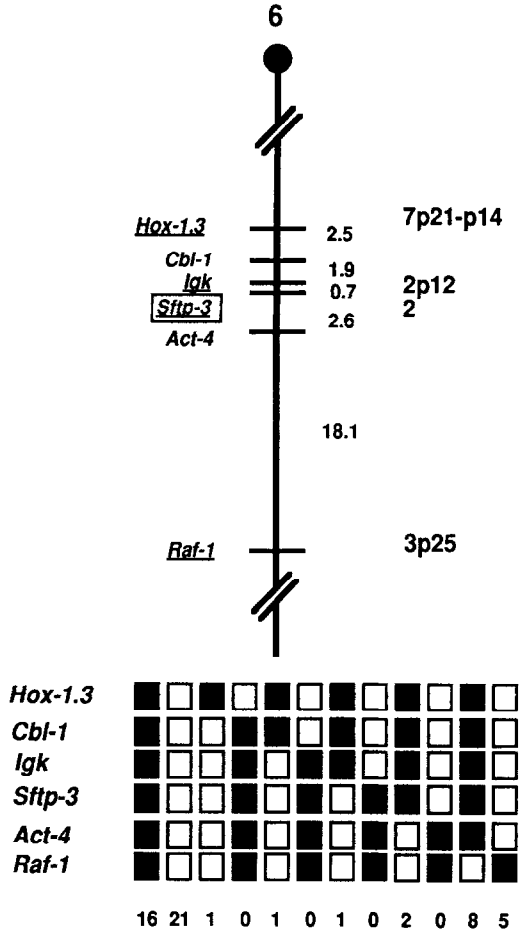

FIG. 2. The chromosomal location and the haplotype data for *Sftp-3* on mouse chromosome 6. See legend to Fig. 1 for description.

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