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Homologs of genes and anonymous loci on human Chromosome 13 map to mouse Chromosomes 8 and 14

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Abstract. To enhance the comparative map for human Chromosome (Chr) 13, we identified clones for human genes and anonymous loci that cross-hybridized with their mouse homologs and then used linkage crosses for mapping. Of the clones for four genes and twelve anonymous loci tested, cross-hybridization was found for six, COL4A1, COL4A2, D13S26, D13S35, F10, and PCCA. Strong evidence for homology was found for COL4A1, COL4A2, D13S26, D13S35, and F10, but only circumstantial homology evidence was obtained for PCCA. To genetically map these mouse homologs (*Cf10, Col4a1, Col4a2, D14H13S26, D8H13S35,* and *Pcca-rs*), we used interspecific and intersubspecific mapping panels. *D14H13S26* and *Pcca-rs* were located on the distal portion of mouse Chr 14 extending by ~30 cM the conserved linkage between human Chr 13 and mouse Chr 14, assuming that *Pcca-rs* is the mouse homolog of PCCA. By contrast, *Cf10, Col4a1, Col4a2,* and *D8H13S35* mapped near the centromere of mouse Chr 8, defining a new conserved linkage. Finally, we identified either a closely linked sequence related to *Col4a2,* or a recombination hot-spot between *Col4a1* and *Col4a2* that has been conserved in humans and mice.

Introduction

Comparative maps are an exceptional resource for identifying candidate genes and models for human genetic diseases and for studying genome organization and evolution (Copeland et al. 1993a). The comparative map for laboratory mice and humans currently consists of more than 1000 genes and conserved anonymous loci (Copeland et al. 1993b; Nadeau et al. 1995). An excellent example of the utility of these maps is the demonstration that the *Pax3* gene is mutated in mice with mutations at the *Splotch* locus (Epstein et al. 1991) and that the human homolog PAX3 is mutated in individuals with Waardenburg Syndrome Type I (Baldwin et al. 1992; Tassabehji et al. 1992). Comparative maps provided the crucial clue: among the many mouse mutations affecting neural crest derivatives in similar ways, only *Splotch* and Waardenburg Syndrome Type I map to homologous locations (Nadeau et al. 1991a). Recent examples of other uses of comparative maps for studying genome organization and evolution are the demonstration that human Chr 2 results from an ancient telomere-telomere fusion (IJdo et al. 1991) and that comparative physical maps generally verify order and relative distances inferred from genetic maps (Kingsmore et al. 1989; Oakey et al. 1992).

Although progress in the development of the comparative map has been considerable with the number of markers in the map doubling the past 30 months, substantial portions of the genome remain poorly defined. An example is the suspected homology between the central-distal portion of human Chr 13 and the central-distal portion of mouse Chr 14 (Nadeau et al. 1992; Copeland et al., 1993b). This suspicion is based on the presence of small clusters of homologous genes that flank both of these chromosome segments (Nadeau et al. 1995). To enhance the comparative map for human Chr 13, we identified and genetically mapped mouse homologs for four human genes and two anonymous DNA loci. Not only were we able to extend the conserved linkage involving human Chr 13 and mouse Chr 14, we identified a new conserved linkage involving human Chr 13 and mouse Chr 8, and found either a new pseudogene or a recombination hot-spot that has been conserved in the two species.

Materials and methods

Genes and anonymous loci. A description of the genes and anonymous loci selected for study is provided in Table 1.

Genetic mapping panels. Two panels were used. The first was an intersubspecific mapping panel prepared by outcrossing (DS/Ei × MOLF/Ei)F_1 females to C3H/HeJ males. DS/Ei is an inbred strain (F55) that is probably homozygous for the *Disorganization* mutation (*Ds;* Chr 14). MOLF/Ei is an inbred strain (F36 + 15) derived from *M. musculus molossinus.* The second panel was an interspecific panel prepared by backcrossing (C57BL/6J × *M. spretus*)F_1 females to C57BL/6J males. Although the *M. spretus* strain was not fully inbred, residual variation is rare (J. Nadeau, unpublished; W. Dietrich and E. Lander, personal communication). This panel has been reported previously (see Nadeau et al. 1990, 1991b and references therein).

Somatic cell hybrid analysis. A mouse-CHO somatic cell hybrid panel (Minna et al. 1975) was used to establish synteny. Occurrence of mouse chromosomes in this panel was previously reported (Popp et al. 1981).

Radiolabeling, Southern transfers, and hybridization. Methods described by Nadeau and Phillips (1987) were used.

Linkage analysis. A multilocus maximum likelihood program was used for calculating the LOD score for order (Nadeau et al. 1991b). This program is based on methods described by Bishop (1985).

Results

Identification of mouse homologs for COL4A1, COL4A2, D13S26, D13S35, F10, and PCCA through cross-hybridization and restric-

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Table 1. Description of clones used for identifying and typing mouse homologs of selected genes and anonymous loci from human Chr 13. Williamson et al. (1991) provide additional documentation of probe and clone characteristics. Bowcock and Taggart (1991), the NIH-CEPH Collaborative Mapping Group (1992), and the Cooperative Human Linkage Center (Buetow et al., 1994) provided documentation for current map localizations.

Gene or anonymous locus	Regional localization	Clone name	Annotation	Reference
COL4A1	q34-qter	HT21	2.7-kb cDNA corresponding to 185 amino acids of the carboxy-terminal Gly-X-Y sequence, all of the carboxy-terminal domain, and the entire 3′ untranslated region of the alpha-1(IV) procollagen mRNA.	Bowcock et al. 1988
COL4A2	q34-qter	HT39	1.7-kb cDNA corresponding to the carboxy-terminal domain and the entire 3′ untranslated region of the alpha-2(IV) procollagen mRNA	Bowcock et al. 1988
D13S3	q33-qter	p9A7	anonymous genomic segment	Bowcock et al. 1991
D13S5	q31-q32	pHUB8	anonymous genomic segment	Bowcock et al. 1991
D13S12	q21	pG18E2-1	anonymous genomic segment	Bowcock et al. 1991
D13S24	—	pG50	anonymous genomic segment	Bowcock et al. 1991
D13S26	q21	pH2-10	anonymous genomic segment	Bowcock et al. 1991
D13S31	q14.3-q21.1	pCRI324	anonymous genomic segment	Bowcock et al. 1991
D13S32	q34-qter	pCRI318	anonymous genomic segment	Bowcock et al. 1991
D13S35	q34	pCRI323	anonymous genomic segment	Bowcock et al. 1991
D13S39	q14.3-q22	WC25	anonymous genomic segment	Bowcock et al. 1991
D13S41	q14.3-q22	WC83	anonymous genomic segment	Leppert et al. 1987
D13S55	q14.3	pCRI-R214	anonymous genomic segment	Bowcock et al. 1991
F10	q34-qter	pcHX14	1.44-kb cDNA corresponding to the leader peptide, the light and heavy chain of the clotting factor, and the 3′ untranslated region	Fung et al. 1985
PCCA	q32	pPCC9-5	2-kb cDNA corresponding to a single open reading frame and including the Ala-Met-Lys-Met codons that distinguish PCCA from PCCB.	Lamhonwah et al. 1986

tion fragment analysis. To identify human clones that cross-hybridize with corresponding sequences in the mouse genome, we selected four genes and twelve anonymous loci for study (Table 1). A clone for each locus was radiolabeled and hybridized to filters onto which endonuclease-digested, size-fractionated genomic DNAs from different strains of inbred mice had been transferred. Strong cross-hybridization was observed for COL4A1, COL4A2, D13S26, D13S35, F10, and PCCA (Fig. 1). For COL4A1, COL4A2, D13S26, D13S35, and F10, single restriction fragments were observed in strains that would subsequently be used for mapping (Table 2). Identification of these single restriction fragments provides strong evidence that the homologous mouse gene or anonymous locus has been identified. We propose the following symbols for the mouse homologs of these genes and anonymous loci: *Cf10, Col4a1, Col4a2, D8H13S35,* and *D14H13S26.* Only PCCA showed multiple fragments in all endonuclease-digested genomic DNAs tested (see Fig. 1F for example). It was, therefore, uncertain which PCCA-related fragment represented the homologous mouse gene. Because of this ambiguity, we designate the mouse PCCA *r*elated *s*equence as *Pcca-rs.*

The weak cross-hybridization for D13S3, D13S5, D13S39, and D13S55 was unreliable for linkage analysis. Cross-hybridization was not detected for D13S12, D13S24, D13S31, D13S32, D13S34, or D13S41. Previous studies showed that 25% to 35% of anonymous human loci have a mouse homolog that can be detected through cross-hybridization (Cheng et al. 1988, 1989). We found reliable cross-hybridization for two of the twelve anonymous loci studied (~17%). This difference was not significantly different from the expected number (3 to 4) of reliably cross-hybridizing clones.

D14H13S26 *and* Pcca-rs *are located on Chr 14, but* Cf10, Col4a1, Col4a2, *and the mouse homolog of D13S35 are not.* To test whether any of these six genes or anonymous loci are located on Chr 14, restriction fragment variants were identified (Fig. 1, Table

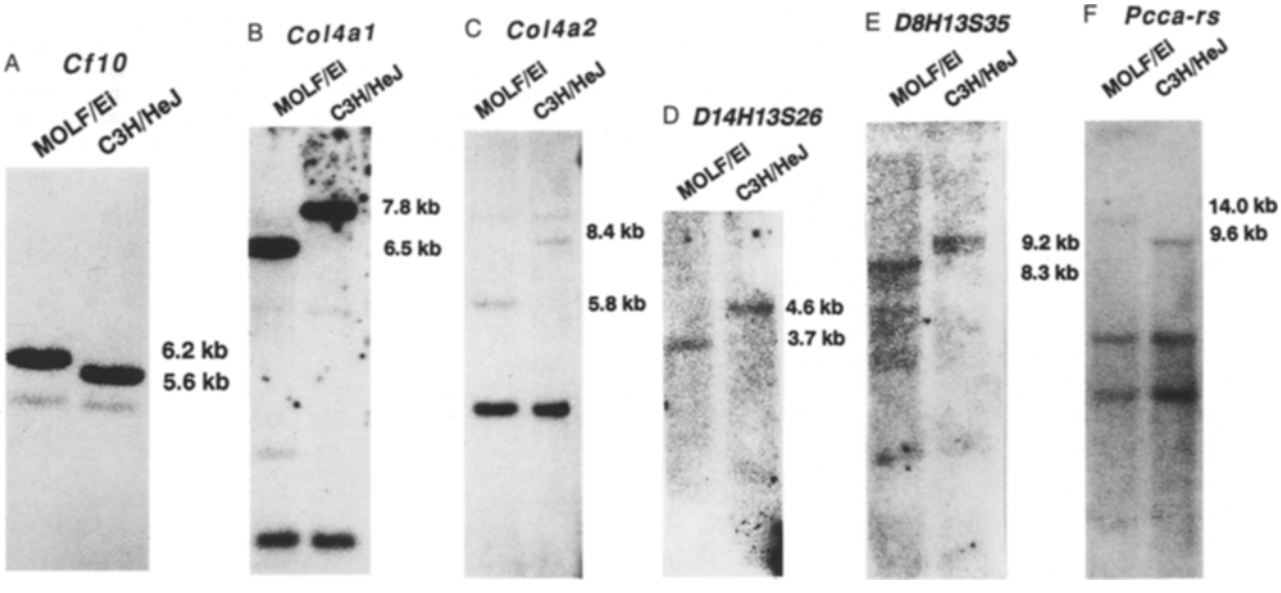

Fig. 1. Representative cross-hybridization patterns of human clones with mouse genomic DNA. A. *Cf10;* B. *Col4a1;* C. *Col4a2;* D. *D14H13S26;* E. *D8H13S35;* and F. *Pcca-rs.*

Table 2. Evidence for homology. Because a single restriction fragment was observed for the restriction enzyme indicated, there is strong evidence that the homologus mouse gene or locus was detected. The exception was PCCA (see text). Emphasis was placed on illustrating single fragments that were used for linkage analysis. 'rs' indicates 'related-sequence'.

Human locus	Strain	Restriction enzyme	Fragment size (kb)	Proposed mouse symbol
COL4A1	BALB/cJ	*Eco*RI	9.8	*Col4a1*
COL4A2	*M. spretus*	*Pst*II	4.0	*Col4a2*
D13S26	MOLF/Ei	*Msp*I	3.7	*D14H13S26*
D13S35	MOLF/Ei	*Msp*I	8.3	*D8H13S35*
F10	*M. spretus*	*Pst*I	3.7	*F10*
PCCA	All enzymes tested produced multiple fragments in each of the mouse strains and restriction enzymes surveyed			*Pcca-rs*

3) and used for following inheritance in the (DS/EiNa × MOLF)F_1 × C3H/HeJ intersubspecific mapping panel. This panel has been typed for more than ~40 genes and anonymous loci on Chr 14 (unpublished). Linkage was detected between *D14H13S26, Pcca-rs,* and several other loci including *Es10* and *Tcra.* Double crossovers were not detected. The LOD score for order was 4.0, providing strong support for the order illustrated in Fig. 2A. These loci extend the conserved linkage by ~30 cM to the distal portion of Chr 14, assuming that *Pcca-rs* is homologous to PCCA (Fig. 3). Unexpected results were obtained for *Cf10, Col4a1, Col4a2,* and the human homolog of D13S35. Homologs for these loci were closely linked to each other, but were not linked to any other locus that has been mapped to Chr 14 (Figure 2B).

Synteny assignment with somatic cell hybrids: Cf10, Col4a1, Col4a2 *and the homolog of D13S35 are located on Chr 4 or Chr 8.* To establish synteny, segregation of mouse-specific restriction fragment length variants for *Cf10, Col4a1,* and *Col4a2* (Table 3) was followed in a panel of 15 somatic cell hybrids. D13S35 was not studied because we assumed that if synteny was found for *Cf10, Col4a1,* and *Col4a2,* the chromosome assignment for the homolog of D13S35 would also be known because these four loci are closely linked. Complete cosegregation was observed between variants for these three loci and mouse Chrs 4 and 8 (results not shown). Ambiguity between these two chromosomes in this hybrid panel has a precedent that was resolved by using an interspecific backcross mapping panel (Nadeau et al. 1990).

Cf10, Col4a1, Col4a2 *and* D8H13S35 *map to the centromeric region of Chr 8.* Restriction fragment length variants for *Cf10* and *Col4a2* (Table 3) were tested for linkage with loci that had been previously mapped to Chrs 4 or 8 in a (C57BL/6J × *M. spretus*)F_1 × C57BL/6J interspecific mapping panel (Nadeau et al. 1990). These two genes showed linkage to genes on the centromeric region of Chr 8 (Fig. 2C). These results establish a new conserved linkage between mouse Chr 8 and human Chr 13 (Fig. 3).

An apparent difference in recombination frequency between the intersubspecific and interspecific crosses. Comparison of recombination frequencies revealed remarkable variation between the intersubspecific and interspecific crosses (Fig. 2B and 2C). In the intersubspecific cross, the corresponding recombination frequency was 17.3%. In the interspecific cross by contrast, *Cf10* and *Col4a2* failed to recombine (N = 60); upper 95% confidence limit for the recombination frequency is 0.049). This difference in recombination frequency was highly significant (chi-square contingency test: $X^2 = 10.1$, $P < 0.001$).

Discussion

The comparative map for human Chr 13. The comparative map for human Chr 13 consisted of a ~2 cM conserved linkage composed of three genes (*Es10,* esterase-10; *Htr2,* seratonin receptor subtype-2; and *Rb1,* retinoblastoma-1) on mouse Chr 14, a shorter conserved linkage composed of two genes (*Gja3,* gap junction membrane channel protein alpha-2; *Gjb2,* gap junction membrane channel protein beta-2) on a separate portion of Chr 14, and a homology segment composed of a single gene (*Flt3,* FMS-like tyrosine kinase-3) on mouse Chr 5 (Nadeau et al. 1992, 1995; Copeland et al. 1993b). Together, these three segments in the mouse correspond to only a small portion of human Chr 13 (Fig. 3). The present study extended, perhaps by ~30 cM, the conserved linkage on mouse Chr 14, assuming that *Pcca-rs* is the mouse PCCA gene (Fig. 3), and identified a new conserved linkage on mouse Chr 8 (Fig. 3). A substantial portion of human Chr 13 is now represented in the comparative map.

Table 3. Restriction fragment variants (RFLVs) used for mapping *Cf10, Col4a1, Col4a2, D8H13S35, D14H13S26,* and *Pcca-rs.* The following abbreviations were used to designate the restriction enzyme (RE) used for defining the RFLV: E, *Eco*RI; M, *Msp*I; P, *Pst*I; S, *Sst*I; and X, *Xba*I. Fragment sizes are given in kilobases. If more than one fragment was detected for a particular locus, the fragment used for following segregation was underlined. The superscripts 's' (for strong) and 'w' (for weak) were used to denote a subjective assessment of the strength of cross-hybridization.

Gene:	*Cf10*	*Col4a1*	*Col4a2*	*D3H13S35*	*D14H13S26*	*Pcca-rs*
Intersubspecific mapping panel:						
DS/Ei	5.2^w, 5.6^s	1.8^w, 7.8^s	3.4^s, 8.4^w, 9.5^w	9.2	4.6	4.2^s, 5.9^s, 9.6^w
MOLF/Ei	5.2^w, $\underline{6.2^s}$	1.8^w, $\underline{6.5^s}$	3.4^s, $\underline{5.8^w}$, 9.5^w	$\underline{8.3}$	$\underline{3.7}$	4.2^s, 5.9^s, $\underline{11.0^w}$
(Enzyme)	(X)	(X)	(X)	(P)	(M)	(M)
Somatic cell hybrids:						
BALB/cJ	$\underline{5.0}$	$\underline{9.8}$	$\underline{2.3, 8.4}$	—	—	—
CHO	$\overline{9.0}$	$\overline{1.7, 2.6}$	$\overline{9.8}$	—	—	—
(Enzyme)	(E)	(E)	(S)			
Interspecific mapping panel:						
C57BL/6J	3.4	—	2.5	—	—	—
M. spretus	$\underline{3.7}$	—	$\underline{4.0}$	—	—	—
(Enzyme)	(P)		(P)			

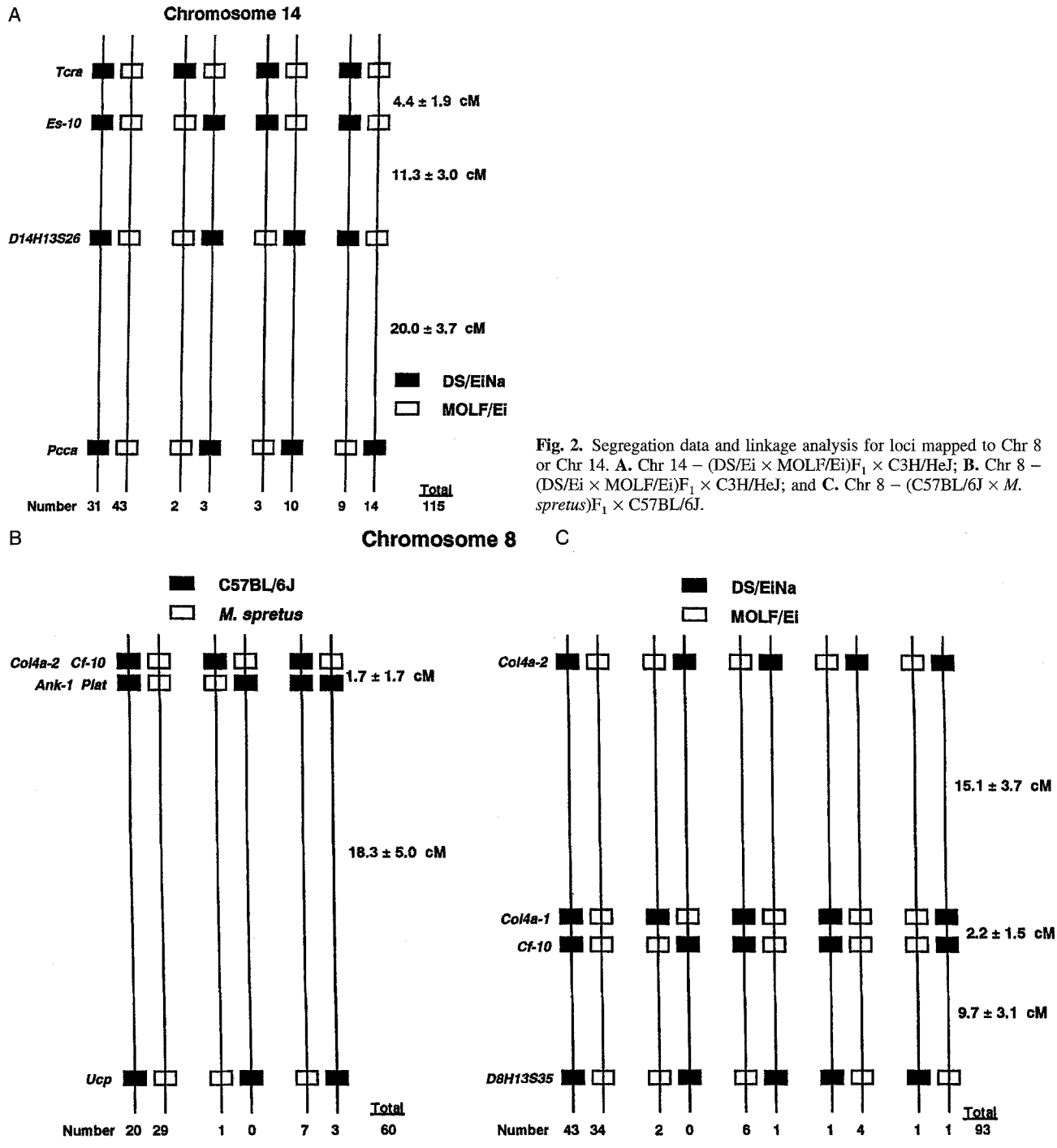

Fig. 2. Segregation data and linkage analysis for loci mapped to Chr 8 or Chr 14. **A.** Chr 14 – (DS/Ei × MOLF/Ei)F_1 × C3H/HeJ; **B.** Chr 8 – (DS/Ei × MOLF/Ei)F_1 × C3H/HeJ; and **C.** Chr 8 – (C57BL/6J × *M. spretus*)F_1 × C57BL/6J.

A COL4A1–COL4A2 recombination hot-spot in humans. The COL4A1–COL4A2 interval in humans has a strong recombination hot-spot. These two genes are less than 400 kb apart, they have a similar head-to-head arrangement, and their transcription start sites may be 42 bp apart (Cutting et al. 1988; Pöschl, et al. 1988; Soininen et al. 1988). Despite their close proximity, the recombination frequency of 2.8% is ~six-fold higher than expected (Bowcock et al. 1988). This is a minimum estimate of hot-spot activity because, if the genes were closer, the magnitude of recombination enhancement would be higher. More importantly, if some chromosomes have recombination hot-spots and others do not, that is, hot-spots are polymorphic in human populations, then pooled data would obscure heterogeneity and lead to underestimates of hot-spot activity. In the CEPH families, two COL4A1–COL4A2 crossovers occurred in the same family (Bowcock et al. 1988), supporting the argument that recombination frequency varies among chromosomes. Absence of detectable linkage disequilibrium is also consistent with a substantial recombination frequency (Bowcock et al. 1988). Mapping results for the mouse suggest a similar recombination hot-spot.

A Col4a2 *pseudogene or a* Col4a1–Col4a2 *recombination hot-spot.* Among the 93 animals typed in the intersubspecific cross, fourteen crossovers were observed between sequences related to COL4A1 and COL4A2, yielding a recombination frequency of 15.1% (Fig. 2C). Physical mapping studies and DNA sequence analysis suggest that this recombination frequency is considerably higher than expected. In the mouse, these genes are arranged head-to-head, transcription start sites are no more than 270 bp apart, and

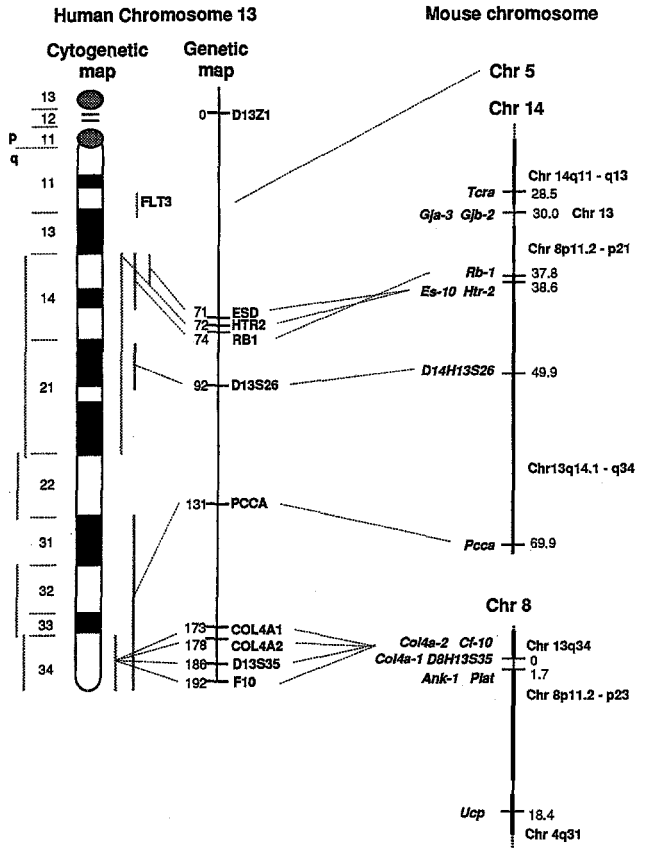

Fig. 3. Consensus comparative map for human Chr 13 and corresponding segments of mouse Chrs 8 and 14. Conserved linkages are highlighted (Nadeau et al. 1992, 1995; Copeland et al. 1993b). Documentation for the human cytogenetic and genetic map localizations is provided by Bowcock and Taggart (1991), the NIH/CEPH Collaborative Mapping Group (1992), and Buetow et al. (1994). D13Z1 is a centromeric marker that was used to anchor the genetic map.

translation initiation codons are separated by 874 bp (Kaytes et al. 1988). A comparable physical arrangement of these genes is found in humans (Cutting et al. 1988; Pöschl et al. 1988; Soininen et al. 1988). If the 5′ ends are approximately 270 bp apart in the mouse as they are in humans (Cutting et al. 1988), then the expected recombination frequency is ~0.20%; 1600 cM in 3×10^9 bp corresponds to an average interval of ~1900 kb between crossovers. The observed recombination frequency was ~76-fold higher than expected.

Two interpretations are possible for the unexpectedly high frequency of recombination between mouse homologs of COL4A1 and COL4A2. The first is that the COL4A2-related sequence that was mapped represents a sequence related to COL4A2, possibly a pseudogene, but not *Col4a2*, itself. This related sequence is by chance linked to the *Col4a2* gene. Inspection of representative restriction fragment patterns showed that the variant fragments that were used for mapping gave a weak hybridization signal; variants for the strongly hybridizing fragments were not detected (Fig. 1 and Table 3). Although single fragments were observed in C57BL/6J and *M. spretus*, two fragments were observed in BALB/cJ, and multiple fragments were found in DS/Ei and MOLF/Ei. Several examples exist of sequences, probably processed pseudogenes, whose occurrence varies among inbred strains of laboratory mice and that are present in some strains and absent in others (Siracusa et al. 1991; Johnson et al. 1992, 1993, 1994; Richards-Smith and Elliott 1992). An alternative explanation is that, as in humans, a recombination hot-spot is located between mouse homologs of COL4A1 and COL4A2, as one is in human (Bowcock et al. 1988).

Alternative gene orders. Depending on the nature of the COL4A2-related sequence that was mapped in the intersubspecific backcross, alternative gene orders are possible. If a COL4A2-related sequence was mapped, the most likely gene order would be *Col4a1–D8H13S35–Cf10–Col4a2-rs*. The *Col4a1–D8H13S35–Cf10* order is consistent with the order in humans (Bowcock et al. 1991; NIH/CEPH Collaborative Mapping Group 1992; Fig. 3). However, if the *Col4a2* gene was mapped, an alternative order is more likely. Close physical proximity of *Col4a1* and *Col4a2* constrains interpretation of the recombination results because insufficient space (<874 bp) is available to position *D8H13S35* and *Cf10* between *Col4a1* and *Col4a2* (Cutting et al. 1988; Pöschl et al. 1988; Soininen et al. 1988). Given this constraint, the more likely order, illustrated in Fig. 3, is ~10^6 more likely than any other order.

Both of these orders suggest an exceptional pattern of crossing-over. Considering the gene order illustrated in Fig. 2C, nine of the fourteen mice with crossovers between *Col4a1* and *Col4a2* also had crossovers between *Col4a1* and *Cf10* or between *Cf10* and *D8H13S35*. As a result, nine mice with double crossovers, but only seven mice with single crossovers, were observed. The double crossover frequency could be higher, because the five mice in which crossing-over was detected only between *Col4a1* and *Col4a2* could have a second crossover distal to *D8H13S35* or more probably proximal to *Col4a2*. The strong possibility therefore exists that crossing-over between *Col4a1* and *Col4a2* is always associated with crossing-over in a flanking interval. As a result, the only mice with single crossovers could be the two with crossovers between *Cf10* and *D8H13S35*. If the alternative order involving a *Col4a1* pseudogene is correct, multiple crossovers are still involved. Other examples of clustered crossovers exist (Nadeau and Phillips 1987; Erhart et al. 1989; Nadeau et al. 1990). More detailed genetic and physical mapping studies involving specific combinations of chromosomes in laboratory mice should resolve this potentially interesting genetic problem.

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