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Genetics

Cognate homeo-box loci mapped on homologous human and mouse chromosomes

(gene mapping/developmental genetics/somatic cell hybrids/blot hybridization/*in situ* hybridization)

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ABSTRACT The homeotic genes of *Drosophila*, which regulate pattern formation during larval development, contain a 180-base-pair DNA sequence termed the "homeo-box." Nucleotide sequence comparisons indicate that the homeo-box motif is highly conserved in a variety of metazoan species. As in *Drosophila*, homeo-box sequences of mammalian species are expressed in a temporal and tissue-specific pattern during embryogenesis. These observations suggest functional homologies between dipteran and mammalian homeo-box gene products. To identify possible relationships between homeo-box genes of mice and humans, we have compared the chromosomal location of homeo-box genes in these species. Using *in situ* hybridization and somatic cell genetic techniques, we have mapped the chromosome 6-specific murine *Hox-1* homolog to the region p14-p21 on human chromosome 7. We have also regionally mapped the murine *Hox-3* locus to 15F1-3 and its human cognate to 12q11-q21. These comparative mapping data indicate that a syntenic relationship in mice and humans is maintained for all homeo-box loci examined to date. We suggest these regions represent evolutionarily conserved genomic domains encoding homologous protein products that function in regulating patterns of mammalian development.

Mammalian homeo-box-containing genes share homologies with homeotic genes of *Drosophila* (1, 2). It has been proposed that these mammalian genes regulate vertebrate development in a manner analogous to that of the homeotic genes in diptera. Recent observations that murine homeo-box sequences are expressed in a temporal and tissue-specific manner during embryogenesis in mice (3–9) and in humans (10) support this notion of functional homologies between dipteran and mammalian homeo-box gene products.

One approach we have employed to identify possible relationships between homeo-box genes of mice and humans is to compare the chromosomal location of homeo-box genes in these species. The cognate *Hox-2* loci have previously been mapped to evolutionarily related regions of mouse chromosome 11 and human chromosome 17, respectively (11, 12). In light of these data, it was of interest to determine if the human homologs of the murine *Hox-1* and *Hox-3* loci similarly mapped to evolutionarily related human chromosomes.

Chromosomal mapping studies place the murine *Hox-1* locus within the proximal region of chromosome 6 (13) and *Hox-3* on chromosome 15 (8). Using *in situ* hybridization and somatic cell genetic techniques, we have localized the human *HOX-1* locus within the region 7p14-p21. We have, in addition, subchromosomally mapped the mouse *Hox-3* locus to bands F1-3 on chromosome 15 and have localized the human *HOX-3* cognate to 12q11-q15. These comparative mapping data extend our previous observation that the cognate *Hox-2* homeo-box loci in mice and in humans are located within evolutionarily conserved genomic domains, to include the homologs of *Hox-1* and *Hox-3*, respectively, and thus indicate that syntenic relationships are maintained at the three homeo-box loci examined to date.

MATERIALS AND METHODS

Cell Lines. JS and PM are karyotypically normal human lymphoblastoid cell lines transformed by Epstein–Barr virus. Primary cultures of murine embryo fibroblasts were derived from 18-day-old BALB/c embryos essentially as described (14). HeLa and A9 are established human and murine fibroblast cell lines, respectively. The cell line 53-87 cl.21 is a human—mouse somatic cell hybrid that contains only human chromosome 7 and the mouse chromosome complement (15).

***In Situ* Hybridization.** Metaphase chromosomes were prepared from karyotypically normal human lymphoblastoid cell lines, JS and PM, using standard methods. Chromosome spreads were G-banded and photographed prior to hybridization. The murine homeo-box-containing plasmid DNA probes pMo-10 (13) and pMo-EA (8) were labeled by nick-translation with 5′-[^{125}I]iodo-2′-deoxycytidine triphosphate (Amersham, 2000 Ci/mmol; 1 Ci = 37 GBq) to a specific radioactivity of 5×10^8 dpm/μg, as was the 3.5-kilobase (kb) *Eco*RI–*Sal* I restriction fragment isolated from the λMo-EA phage (8). *In situ* hybridization was performed as previously described (16). Slides were autoradiographed for 1–6 weeks, depending on the probe used.

Southern Blot Hybridization. HeLa, A9, and 53-87 cl.21 DNA was digested with the restriction enzyme *Eco*RI, electrophoresed through 0.8% agarose gel, and transferred to nitrocellulose (17). The probe DNA was nick-translated to a specific radioactivity of 10^8 cpm/μg with [^{32}P]dCTP (Amersham). Hybridization was carried out at high stringency in 5× SSC (1× SSC is 0.15 M NaCl/0.015 M trisodium citrate) containing 0.1% $NaDodSO_4$, 10% (wt/vol) dextran sulfate, and 1 mg/ml each of bovine serum albumin, Ficoll, and polyvinylpyrrolidone at 65°C. After hybridization, filters were washed to 65°C in 0.1× SSC and 0.1% $NaDodSO_4$ and exposed to Kodak XAR-5 film for 12–48 hr at −70°C. Hybridization conditions employed with the pG10 UPA probe, which contained a 1.4-kb *Hin*dIII restriction fragment derived from the 5′ region flanking the pMo-10 homeo-box, were identical except that the hybridization and wash temperature was 55°C.

RESULTS

Human *HOX-1* Mapping. The human *HOX-1* cognate locus was mapped by using the murine homeo-box probe pMo-10. After *in situ* hybridization, the distribution of silver grains

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Abbreviation: kb, kilobase(s).

observed over 205 previously photographed human chromosome spreads was plotted on a computer-generated representation of the human haploid karyotype. Background labeling averaged 3.5 grains per unit chromosome length, somewhat higher than generally observed with ^{125}I-labeled probes, but a difference ascribed to the long exposures (up to 6 weeks) required to detect a signal when the heterologous murine pMo-10 homeo-box clone was used. Two primary sites of labeling were detected, one each on chromosomes 7 and 17 (Fig. 1). Of 849 autoradiographic silver grains located on chromosomes, 64 (7.5%) were specifically localized within the region 7p14-p22, while 31 (3.7%) were observed at 17q11-q22. Statistical evaluation by Poisson distribution of the number of grains per unit chromosome length indicated that labeling at these loci was significant ($P << 0.001$). The localization of homeo-box hybridization on chromosome 17 is precisely consistent with that previously observed (11) by using the human-specific *HOX-2* probes Hu-1 and Hu-2 (18), and it serves as an internal positive control for homeo-box hybridization.

The human *HOX-1* localization on chromosome 7 was confirmed by blot hybridization of ^{32}P-labeled pMo-10 to DNA prepared from a human–mouse hybrid somatic cell line, 53-87 cl.21, which contains a full complement of mouse chromosomes but only human chromosome 7 (ref. 15; data not shown). Mouse A9 and human HeLa cell DNA were used as controls. Species-specific bands of 1.4 and 2.1 kb were observed for mouse and human DNA, respectively. The hybrid cell line was positive for both the 1.4-kb mouse band and the 2.1-kb human band, confirming that the human *HOX-1* locus resides on chromosome 7. Although this experiment was performed under stringent hybridization conditions, we felt it necessary to rule out the possibility that the pMo-10 probe might be hybridizing to homeo-box sequences related to but distinct from those within the *HOX-1* locus. Blot hybridization analyses were therefore repeated with the pG10 UPA probe, which does not contain a homeo-box sequence. The results of this experiment are shown in Fig. 2. The data are identical to those observed with the pMo-10 probe and thus are consistent with our assignment of the human *HOX-1* locus to chromosome 7. We conclude on the basis of the previous assignment of the murine *Hox-1* locus to the proximal region of mouse chromosome 6 (13), and data presented here, that the cognate *Hox-1* loci of mice and humans reside within homologous chromosomal regions.

The *HOX-1* locus maps in proximity to the gene encoding epidermal growth factor (EGF) (19), which is amplified in the human epidermoid carcinoma cell line A431 (20–22). Since amplification domains may approach the size of a chromosome band (23), we probed A431 cell DNA on a Southern blot with the pMo-10 probe to test whether *HOX-1* DNA sequences were coamplified with the EGF receptor gene in this tumor cell line. Our results (not shown) rule out coamplification of pMo-10 and EGF receptor DNA sequences, indicating that *HOX-1* lies outside of the amplified domain of chromosome 7 in A431 cells.

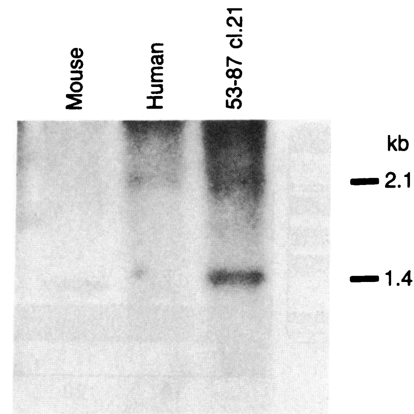

FIG. 2. Southern blot hybridization of the pG10 UPA probe to *Eco*RI-cleaved genomic DNA from HeLa (human control), A9 (mouse control), and 53-87 cl.21 cells. Molecular sizes of human and mouse pG10 UPA-hybridizing bands are indicated at the right.

Mapping the Murine and Human *Hox-3* Homologs. The murine *Hox-3* probe pMo-EA was hybridized to chromosomes prepared from primary cultures of mouse embryo fibroblasts and identified by G-banding prior to hybridization. After autoradiography, the distribution of silver grains from 39 metaphase spreads was plotted on a computer-generated histogram in which a standard idiogram of the haploid mouse karyotype (24) was divided into 156 units, each proportional to an average grain diameter of 0.35 μm (data not shown). The background labeling was low, averaging 2.5 grains per unit chromosome length. Of 397 silver grains observed over chromosomes, 48 (12%) were located on chromosome 15. A total of 33 (69%) of the chromosome 15-specific grains were localized to the region F1-3 (Fig. 3*a*), which represents approximately 0.6% of the haploid murine genome length. Statistical evaluation, by Poisson distribution, of the number of grains per unit chromosome length indicated that these data were statistically significant ($P << 0.001$).

The human *HOX-3* homolog was mapped by *in situ* hybridization using a 3.5-kb *Eco*RI–*Sal* I restriction fragment probe located 6 kb downstream from the Mo-EA homeo-box (8). The distribution of autoradiographic silver grains observed over 61 chromosome spreads was plotted on a histogram representing the haploid human karyotype as described above (data not shown). A total of 553 grains were

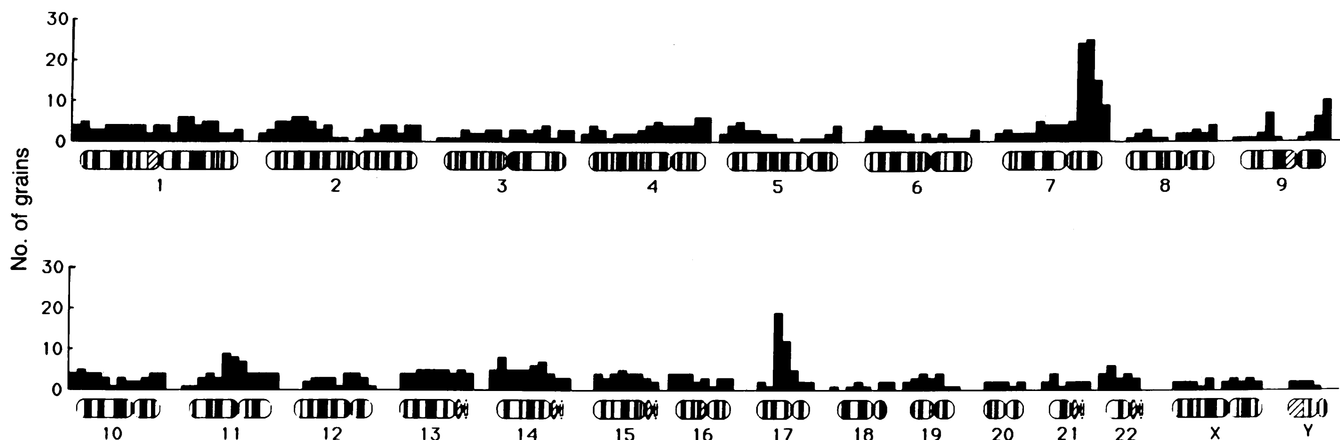

FIG. 1. Localization of the human *HOX-1* homolog to human chromosome 7p14-p21.

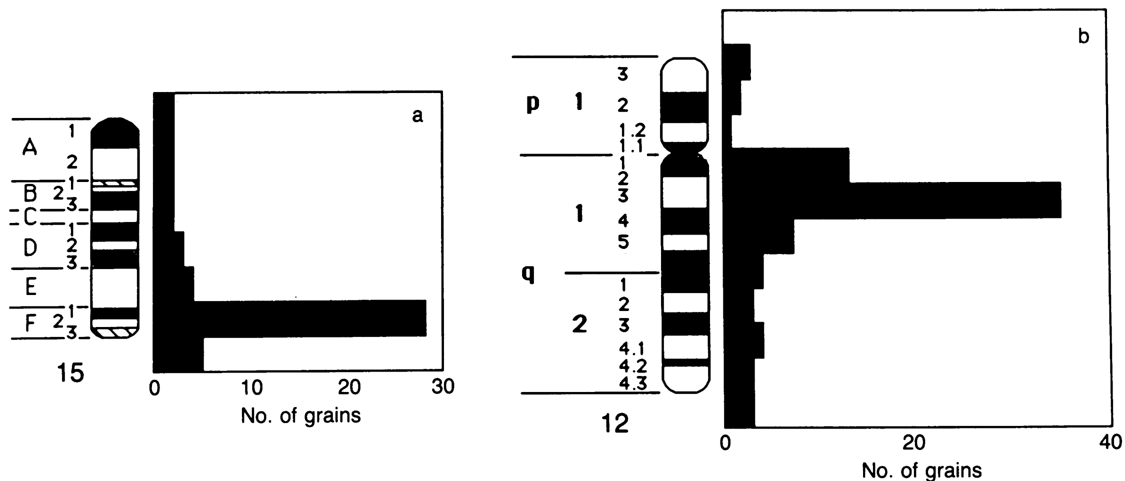

FIG. 3. Localization of (a) the murine *Hox-3* locus to 15F1-3 and (b) the human *HOX-3* homolog to 12q11-q15.

observed on chromosomes, of which 78 (14%) were present on chromosome 12. Of the chromosome 12-specific grains, 70% were localized within the region q11-q15 (Fig. 3b). Localization was statistically significant ($P << 0.001$) by criteria stated above. No additional sites were detected, in agreement with the observation of a single hybridizing *Eco*RI restriction fragment in genomic Southern blots (data not shown). These data indicate that as with *Hox-1* discussed above, and as previously reported for *Hox-2* (11, 12), the *Hox-3* loci of mice and humans are also maintained within evolutionarily conserved chromosomal regions.

DISCUSSION

The Human *HOX-1* Locus Maps to Region 7p14-p21. *In situ* hybridization using the murine pMo-10 homeo-box probe maps the human *HOX-1* locus to 7p14-p21. The chromosomal assignment was confirmed by Southern blot hybridization of murine *Hox-1*-specific probes to a human–mouse somatic cell hybrid containing only human chromosome 7 and a full complement of mouse chromosomes. In addition to the site on chromosome 7, a second labeled site was observed at 17q21-q31, consistent with our previous localization of the human *HOX-2* locus (11). Multiple homeo-box domains have been molecularly defined within both the murine (4, 5) and human (5, 18) *Hox-2* loci. Since the DNA regions flanking the *HOX-2* homeo-box domains on human chromosome 17 are not detectably homologous to the DNA flanking the pMo-10 homeo-box (data not shown), the autoradiographic signal observed on chromosome 17 probably results from hybridization of the 180-base-pair murine homeo-box sequence within the pMo-10 probe to repetitive human homeo-box sequences at this chromosomal site. Reiterated homeo-box domains have been detected within the murine *Hox-1* region (25); however, the human *HOX-1* locus has been less well characterized. Considering the relative signal intensities at the two sites, it is likely that the labeling observed over 7p14-22 results from hybridization extending to homologous DNA sequences flanking the Mo-10 homeo-box. This conclusion is consistent with results of Southern blot analyses using the pG10 UPA probe, which does not contain a homeo-box sequence.

Comparative gene mapping data define conserved linkage relationships between species. The murine *Hox-1* locus maps to the proximal region of chromosome 6 (13). The human cognate *HOX-1* locus maps to 7p14-p21. Conservation of gene linkage associations is observed around the *Hox-1* locus on mouse chromosome 6 and human chromosome 7 (Fig. 4 a and b). The *Hox-1* locus and the genes encoding the T-cell antigen receptor β-chain gene (26), trypsin (27), and carboxypeptidase A (28) all reside on murine chromosome 6. In humans, the *HOX-1* locus maps to the short arm of chromosome 7. The T-cell antigen receptor β-chain (26, 29–33) and trypsin (34) genes map to the long arm of chromosome 7. Carboxypeptidase A has also been assigned to human chromosome 7 (28). Although these genes are maintained on chromosome 7, it is not possible, given available mapping data, to discern whether they are part of a single linkage group spanning the centromere of this chromosome or if they represent separated linkage groups conserved on mouse chromosome 6.

Cognate *Hox-3* Loci Map to Evolutionarily Related Mouse and Human Chromosomes. The murine *Hox-3* probe pMo-EA was previously assigned to mouse chromosome 15 by analysis of a panel of somatic cell hybrids (8). By using *in situ* hybridization, the *Hox-3* locus has been regionally mapped to 15F1-3 (Fig. 4*f*). The murine mammary tumor virus integration locus, *int-1*, maps within this same region (S. Adolf, C. R. Bartram, and H. Hameister, personal communication). The human *HOX-3* cognate has been localized to 12q11-q15 (Fig. 4*e*), overlapping the map locus of the human homolog of *INT1* at 12pter-q14 (35). Mouse chromosome 15F therefore appears to be homologous to a region including pter-q15 on human chromosome 12. The genes encoding elastase-1 and glycerol-3-phosphate dehydrogenase also reside on murine chromosome 15 and human chromosome 12 (36). It is likely that an evolutionarily conserved linkage group composed of *Hox-3, int-1*, and the genes for elastase-1 and glycerol-3-phosphate dehydrogenase maps to murine chromosome 15F and human chromosome 12pter-q15.

In addition to the relationships we observed between homologous mouse and human chromosomes discussed above, we also noticed relationships among the human chromosomes on which the *HOX-1, HOX-2*, and *HOX-3* loci reside. The human *HOX-1* locus maps in proximity to the human homolog of the avian erythroblastosis virus oncogene, *erbB1*, on chromosome 7 (refs. 37 and 38; Fig. 4*a*). The human *HOX-2* locus is located within a region on chromosome 17 at which reside two related oncogenes, *erbA1* and *erbB2* (refs. 38–40; Fig. 4*c*). It is of interest to note that in mice the homologous *erbA* and *erbB* oncogenes are syntenic with the *Hox-2* locus on chromosome 11 (refs. 11, 12, and 38; Fig. 4*d*). Similarly, two evolutionarily related peptide hormones, neuropeptide Y and pancreatic polypeptide, map to human chromosomes 7 and 17, respectively (ref. 41; Fig. 4 *a* and *c*). In addition, two related serine protease genes, trypsin and elastase, are located on human chromosomes 7 and 12 (34) and on the homologous chromosomes 6 and 15 in the

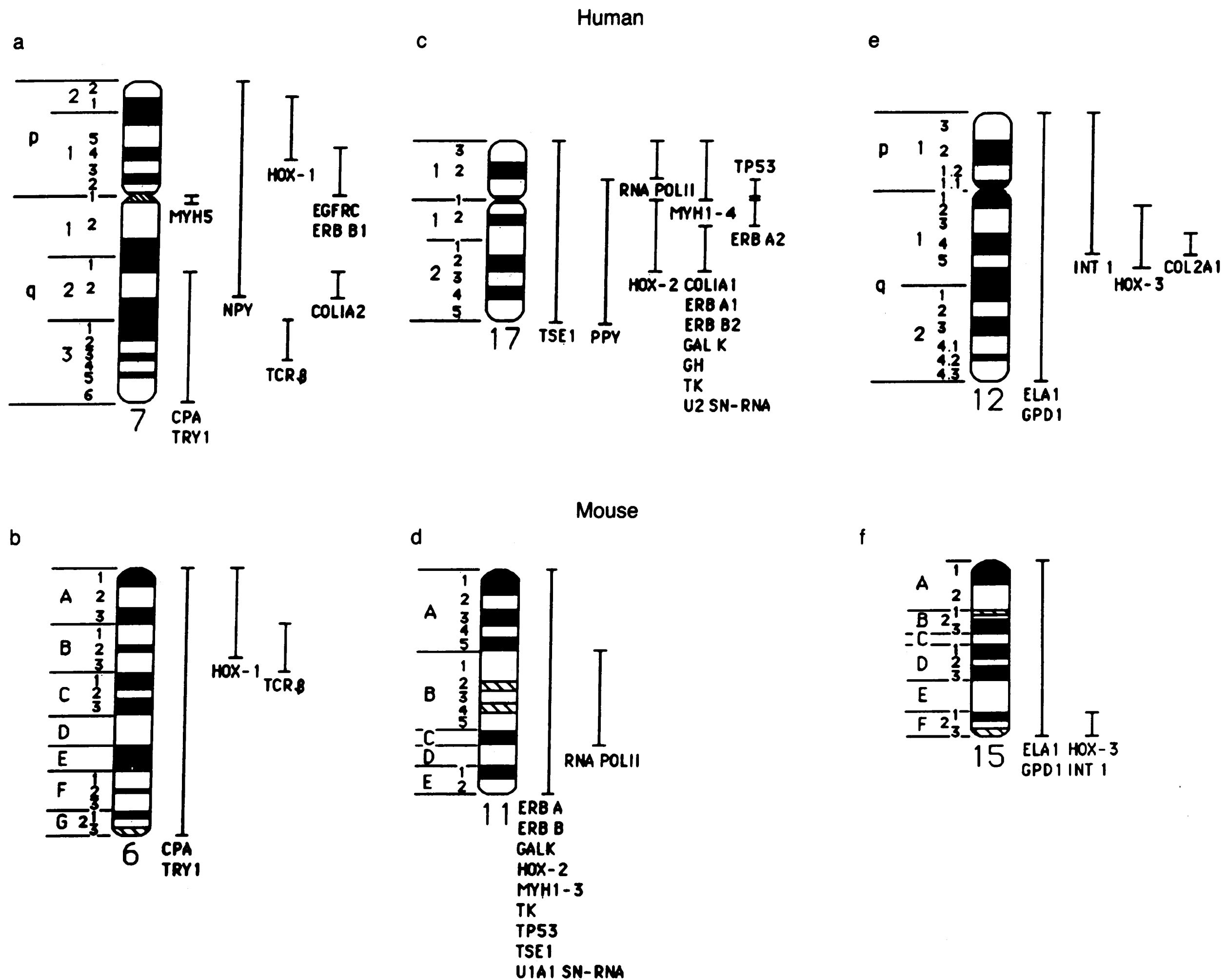

FIG. 4. Conservation of *Hox-1* and *Hox-2* associated gene linkage relationships on human chromosomes 7 (*a*), 17 (*c*), and 12 (*e*) and mouse chromosomes 6 (*b*), 11 (*d*), and 15 (*f*). Gene symbols: *COLIA1*, collagen type I α1; *COLIA2*, collagen type I α2; *COL2A1*, collagen type 2 α1; *CPA*, carboxypeptidase A; *EGFRC*, epidermal growth factor receptor; *ELA1*, elastase-1; *ERB A1, ERB A2, ERB B1*, and *ERB B2*, avian erythroblastosis virus and related cellular oncogene homologs; *GALK*, galactokinase; *GH*, growth hormone; *GPD*, glycerol-3-phosphate dehydrogenase; *HOX-1, HOX-2*, and *HOX-3*, homeo-box loci *1, 2*, and *3*; *INT1*, mouse mammary tumor virus integration locus; *MYH1-5*, myosin heavy chain genes *1-5*; *NPY*, neuropeptide Y; *PPY*, pancreatic peptide; *RNA POLII*, RNA polymerase II 215-kilodalton subunit; *TCRβ*, T-cell antigen receptor β-chain; *TK*, thymidine kinase; *TP53*, tumor antigen p53; *TRY1*, trypsin 1; *TSE1*, tissue-specific extinguisher 1; *U1A1* and *U2 SN-RNA*, small nuclear RNA species.

mouse, respectively (27). We also note that in each of the human homeo-box-containing linkage groups discussed above are members of the collagen gene family (refs. 42–48; Fig. 4 *a, c*, and *e*). The significance of these correlations is unclear, but it is unlikely in our view that they are purely coincidental.

The role of the *Hox* loci in mammalian development is of interest in light of the function proposed for homeo-box gene products of *Drosophila*. Homeotic mutations analogous to those identified in *Drosophila* have not, however, been documented in mice or humans. Human epithelial heteroplasias and metaplasias have been suggested to be analogous to homeotic transformations (49). In mice, trisomies of all but chromosome 19 are lethal, due to developmental defects during embryogenesis. The extent of developmental retardation correlated with trisomies of chromosomes 6, 11, and 15, however, is among the most severe relative to other trisomic states (50). Whether developmental defects associated with these trisomies in particular are related to dosage effects involving homeo-box genes or to involvement of unrelated genes located on the same chromosomes is currently unclear. Also of interest with respect to the possible function of the homeo-box genes are a number of morphologic mutations that map specifically to the distal region of mouse chromosome 15. Most notable is the semidominant velvet coat (*Ve*) mutation (51). Homozygous *Ve/Ve* embryos are characterized by severe neural tube defects, and they die at 8–9 days of gestation. It should be informative to test for allelic identity between *Hox-3* and *Ve*.

Data presented in this report demonstrate that the three homeo-box loci *Hox-1, Hox-2*, and *Hox-3* are maintained on homologous chromosomes both in mice and in humans. We suggest that the syntenic relationships observed on the respective chromosome homologs reflect evolutionary conservation of the homeo-box-containing linkage groups. Implicit in such an explanation is a conservation of function of the protein coding regions of these domains. Whether this pattern of conserved linkage associations has a functional significance, however, remains a matter of conjecture.

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