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Lengths of chromosomal segments conserved since divergence of man and mouse

(linkage maps/linkage homology/chromosome rearrangement/probability of linkage conservation/rate of chromosomal evolution)

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ABSTRACT **Linkage relationships of homologous loci in man and mouse were used to estimate the mean length of autosomal segments conserved during evolution. Comparison of the locations of >83 homologous loci revealed 13 conserved segments. Map distances between the outermost markers of these 13 segments are known for the mouse and range from 1 to 24 centimorgans. Methods were developed for using this sample of conserved segments to estimate the mean length of all conserved autosomal segments in the genome. This mean length was estimated to be 8.1 ± 1.6 centimorgans. Evidence is presented suggesting that chromosomal rearrangements that determine the lengths of these segments are randomly distributed within the genome. The estimated mean length of conserved segments was used to predict the probability that certain loci, such as peptidase-3 and renin, are linked in man given that homologous loci are *x* centimorgans apart in the mouse. The mean length of conserved segments was also used to estimate the number of chromosomal rearrangements that have disrupted linkage since divergence of man and mouse. This estimate was shown to be 178 ± 39 rearrangements.**

Recent progress in mammalian genetics has permitted the chromosomal assignment of numerous biochemically defined loci and the development of linkage maps for a variety of species (1–4). Analysis of these linkage maps provides a useful means for studying genomic organization and evolution. For example, linkage of homologous loci on the X chromosome has been rigorously conserved in mammals, suggesting that chromosomal rearrangements involving the X chromosome and autosomes have been rejected by natural selection (5, 6). By contrast, analyses of conserved and disrupted autosomal linkages show that closely linked loci in one species tend to be linked in other species and loci that are loosely linked in one species tend to be unlinked in other species (7). It is not known, however, whether conserved segments are protected from chromosome rearrangement and may therefore represent adaptive combinations of loci or whether conserved segments reflect a random distribution of chromosomal rearrangements within the genome.

Linkage maps for man and mouse are now sufficiently complete to warrant more quantitative analyses of the extent of linkage conservation and evaluation of a number of arguments concerning genomic organization and evolution. Perhaps the most useful parameter in these analyses is the length of conserved segments. There are two problems in calculating the lengths of these segments, however. The first is that the lengths of identified conserved segments are not precisely known because the lengths are probably greater than the distance between the outermost markers defining the segments. The second problem is that such lengths are based on segments marked by two or more homologous markers; segments lacking identified markers and segments with a single identified marker are necessarily excluded from these analyses. Because large segments are more likely to contain two or more markers than are small segments, the sample of identified conserved segments is biased toward larger segments. We here present methods to account for these problems and apply these methods to linkage data for homologous autosomal loci in man and mouse. In addition, we show that the lengths of conserved segments can be used for calculating the probability of linkage for unmapped loci and for estimating rates of chromosomal evolution.

IDENTIFICATION OF CONSERVED AUTOSOMAL SEGMENTS

Davisson and Roderick (1), Keats (2), Pearson *et al.* (3), and Womack (4) have presented summaries of the linkage maps for man and mouse. These data have been augmented with several recently mapped loci (Fig. 1). Identification of homologous loci is based on the biochemical functions of the corresponding gene products. Homologous loci are regarded as markers for the chromosomal segments in which they are carried, and the term *marker* is used to designate homologous loci whose murine member has been mapped and whose human member has at least been assigned to a specific chromosome.

Eighty-three homologous loci have been assigned to specific autosomes in man and mouse (Fig. 1). These loci consist of two groups, one group of 54 loci whose chromosomal locations have been determined in the mouse through identification of genetic variants and conventional linkage studies—e.g., isocitrate dehydrogenase-1 (*Idh-1*) and peptidase-3 (*Pep-3*)—and another group of 29 loci that have been assigned to a specific chromosome but have not been precisely mapped within the associated linkage maps—e.g., acid phosphatase-2 (*Acp-2*) and adenylate kinase-2 (*Ak-2*). The 54 loci identify 36 homologous segments and the 29 loci, another 10 homologous segments. Thus, a minimum estimate of the total number of homologous segments is 46.

ASSUMPTIONS OF THE ANALYSIS

The assumptions made in the analysis presented below and the evidence concerning these assumptions are the following. The first assumption is that synteny of two or more markers in both species is presumptive evidence for linkage conservation. There are three arguments supporting this assumption: (*i*) the lengths of segments are relatively short, (*ii*) similar linkage arrangements are found in many other mammalian species, and (*iii*) the *a priori* probability is small either that markers originally unlinked in the last common ancestor of man and mouse have become linked in both species or that linkage has been disrupted and then reestablished.

The second assumption is that autosomal rearrangements fixed during evolution are randomly distributed within the genome. Although it is recognized that certain rearrange-

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Abbreviations: CM, centimorgan(s); myr, million years.

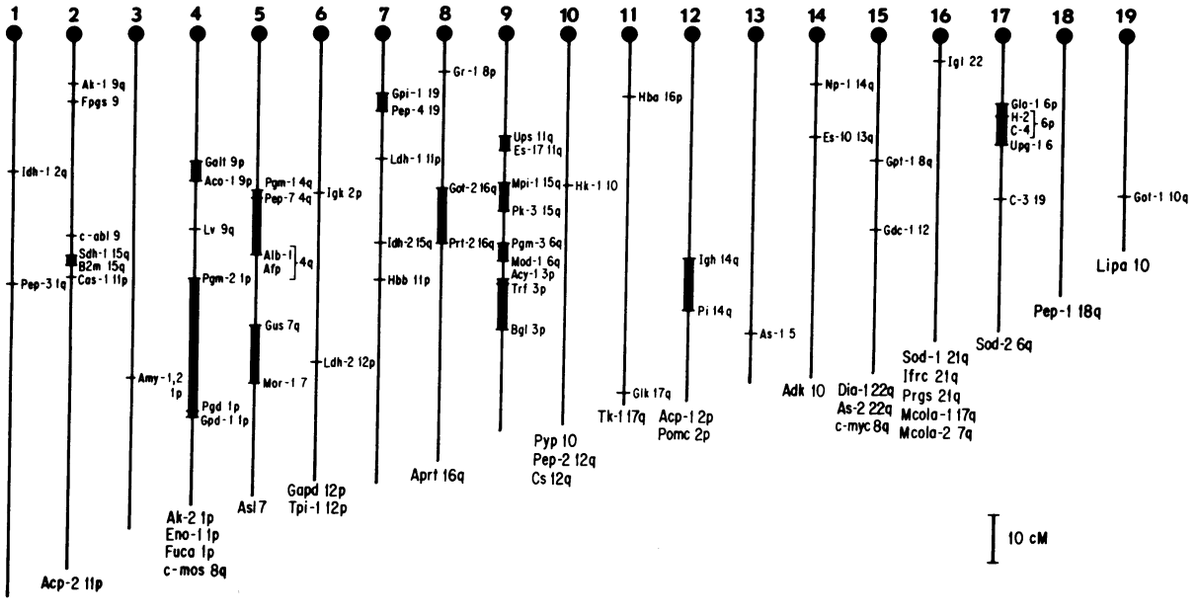

FIG. 1. Locations in the mouse linkage map of autosomal loci whose human homologues have been assigned to specific chromosomes. Conserved segments are indicated by heavy lines. The chromosomal location of each locus in man is given after each mouse symbol. Nomenclature is defined in ref. 8 (pp. 6–42) except for the following (mouse nomenclature has been used): cellular Abelson murine leukemia viral oncogene, c-*abl*; cellular Moloney sarcoma viral oncogene, c-*mos*; cellular avian myelocytomatosis viral oncogene, c-*myc*; catalase-1, *Cas-1* (previously named *Cs-1*); citrate synthase, *Cs*; folylpolyglutamyl synthetase, *Fpgs*; α-L-fucosidase, *Fuca*; type 1 procollagen pro α_1 and pro α_2, *Mcola-1*, *Mcola-2*; α_1-antitrypsin, *Pi*; proopiomelanocorticotropin, *Pomc*; phosphoribosyl glycinamide synthetase, *Prgs*; chymotrypsinogen B, *Prt-2*. References to many of the loci mapped in the mouse can be found in refs. 1–4 and 9; references for the remaining genes are the following: *Aco-1* (10), *Es-17* (11), *Fpgs* (12), *Galt* (10), *Idh-2* (13), *Mcola-1* (14), *Mcola-2* (14), and *Pi* (15). References to many of the loci mapped in man can be found in refs. 1–4 and 9; references for the remaining loci are the following: *Adk* (16), *Afp* (17), *Asl* (18), *C-3* (19), *C-4* (20, 21), *Cs* (22), *Dia-1* (23), *Es-10* (24), *Fpgs* (25), *Gdc-1* (26), *Got-2* (27), *Ifrc* (28, 29), *Lipa* (30), *Lv* (31), *Prgs* (32), *Sdh-1* (33), *Upg-1* (34), and *Ups* (35). The references given above are meant to provide access to the relevant literature and are not intended to be exhaustive or to assign priority. Although *Ak-1* and *Fpgs* have been assigned to the centromeric end of mouse chromosome 2, their precise locations have not been determined. For this reason *Ak-1* and *Fpgs* have not been used in calculations involving *D*, *G*, or *L*. Although *Aco-1*, *Galt*, and *Lv* are syntenic in man and mouse, *Lv* was not included as part of the conserved segment marked by *Aco-1* and *Galt* because *Lv* and *Aco-1*/*Galt* are located on alternative chromosome arms in man.

ments occur more frequently than others, it is doubtful that such nonrandomness would materially affect the overall distribution of conserved segment lengths. If, however, rearrangements are not permitted in large chromosomal regions, then deviations from a random distribution of conserved segment lengths should be evident.

The third assumption is that crossovers are randomly distributed within the genome such that map distance reflects physical distance. The nonrandom distribution of chiasmata suggests that recombination frequency is not strictly proportional to physical chromosome length throughout the mouse genome (36). As a result, recombination frequencies may underestimate physical length in some parts of the genome and overestimate it in other parts. Consequently, the lengths of certain conserved segments might be overestimated and the length of others, underestimated. The effects of such distortion would be to increase the variance of conserved segment lengths. Variation in chiasmata frequency is not extreme, however, and therefore this third assumption seems acceptable for the purposes of obtaining a provisional estimate of the mean conserved segment length.

The fourth assumption is that the distribution of homologous markers in the genome is random and independent. In general, the availability of markers probably depends more on technical factors such as the existence of a specific stain for detecting isozymic variation or the expression of loci in somatic cell hybrids than on the location of a locus in the genome. Members of gene complexes cannot be viewed as independently ascertained and distributed, however. In most cases, these complexes consist of closely linked loci whose functions are related and whose members are probably gene duplicates. Examples of such loci are the β-globin genes (37) and albumin and α-fetoprotein (38). Therefore, gene complexes were counted as a single marker. In other cases, the number of markers that should be counted is not clear. The major histocompatibility complex (*Mhc*), for example, consists of at least three groups of loci involved in immune response (39). Two groups show both nucleic acid and protein homology; the third group, *C-4* (complement component 4), *Bf* (properdin factor B), and *Slp* (sex-limited protein), shows little homology to the other two groups. We have arbitrarily counted the *Mhc* as two markers; *H-2* representing the class I and II loci and *C-4* representing the class III loci (39). In general, few arbitrary decisions such as these were necessary.

THE LENGTHS OF CONSERVED SEGMENTS

Recombination frequencies are known for 13 of the 36 homologous segments (Table 1). The average map distance between the outermost markers of these segments is 8.5 centimorgans (cM) (SD, 6.0 cM); the shortest distance is about 1 cM, the longest is about 24 cM.

We wished to calculate the expected value of the length of a conserved segment (m) relative to the distance or range (r) between the outermost of n markers ($n \geq 2$). Because individual homologous markers are assumed to be randomly distributed within the segment, the statistical problem is equivalent to determining the expected range of a random sample taken from a uniform distribution [$u(x) = 1/m$, $0 < x < m$; $u(x) = 0$ for all other values of x]. The mathematical expectation of the range (r) can be derived as follows. n randomly distributed markers divide a segment of length m into $n + 1$ intervals, each of which has an expected length $m/(n + 1)$. There are $n - 1$ intervals between the outermost markers; hence, the mean length between them is $n - 1$ times as great

Table 1. Lengths of homologous autosomal chromosomal segments in mouse and man

Gene combination	Length of segment, cM		Chromosome	
	r*	m	Mouse	Human
B2m and *Sdh-1*	1	3	2	15q
Galt and *Aco-1*	5	15	4	9p
Pgm-2, *Pgd*, and *Gpd-1*	24	48	4	1p
Pgm-1, *Pep-7*, and *Alb-1(Afp)*	12	24	5	4q
Gus and *Mor-1*	11	33	5	7q
Gpi-1 and *Pep-4*	4	12	7	19
Got-2 and *Prt-2*	10	30	8	16q
Ups and *Es-17*†	3	9	9	11q
Mpi and *Pk-3*	6	18	9	15q
Pgm-3 and *Mod-1*	3	9	9	6q
Acy-1, *Trf*, and *Bgl*	10	20	9	3p
Igh and *Pi*	12	36	12	14q
Glo-1, *H-2*, *C-4*, and *Upg-1*	9	15	17	6p

*Recombination frequencies (RF) for heterozygous male mice are given. References to the original recombination studies can be found in Davisson and Roderick (1). In some cases, RFs were available for females only or for males and females combined. Because there is a slight but nonsignificant tendency (sign test, $P > 0.05$, $N = 157$) for RFs to be higher in females than in males (males, mean RF = 13.4 cM; females, mean RF = 15.2 cM), RFs for females only or for males and females combined were not used directly. Instead, RFs for females were multiplied by (13.4/15.2) and for males and females combined by (13.4/14.3) to convert the RF to an estimated RF for males. In general, these adjustments did not appreciably alter the original RF. r is the distance or range between the outermost loci marking a conserved segment and m is the expected value of the length of a conserved segment.

†T. K. Antonucci, O. von Deimling, and M. Meisler, personal communication.

as between adjacent markers. Therefore, the expected value of r is

$$E(r) = m(n - 1)/(n + 1). \quad [1]$$

By inverse estimation, the length of a particular segment ($\hat{m}$) is given by

$$\hat{m} = r(n + 1)/(n - 1). \quad [2]$$

Eq. 2 was used to transform the range (r) of each segment to an estimate of the length of each conserved segment (Table 1). The mean of the transformed ranges was 20.9 cM (SD, 12.8 cM).

Because conserved segments were identified by the presence of two or more linked homologous markers, segments lacking identifiable markers and segments with a single identifiable marker were necessarily excluded in estimates of conserved segment length. As a result, the estimate of the mean transformed segment length (the mean of $\hat{m}$s) is biased toward long segments. Account for this bias was made in the following way. Let x' be a random variable representing the length of a conserved segment detected by virtue of its containing two or more homologous markers. We wished to obtain the expected value of the transformed sample mean $[E(x')]$ in terms of the actual mean segment length, L. The probability that a segment of size x contains two or more markers and was thus included in the sample is given by the truncated Poisson distribution

$$\sum_{k=2}^{\infty} \frac{(Dx)^k}{k!} e^{-Dx}, \quad [3]$$

which is equal to

$$1 - e^{-Dx} - Dxe^{-Dx}, \quad [4]$$

where $D = T/G$—i.e., the density (D) is equal to the total number of mapped homologous markers (T) divided by the genome size (G), where G is measured in centimorgans. The relative frequency of segments of size (x) in the sample is given by

$$S(x) = [1 - e^{-Dx} - Dxe^{-Dx}]f(x)dx, \quad [5]$$

where $f(x)$ is the probability density function of x throughout the genome. Because L has been defined as the mean length of conserved segments, it follows that the frequency of rearrangements per unit chromosome length is $1/L$ (cf. p. 22 of ref. 40). The probability of no rearrangement within a segment of unit length is $e^{-1/L}$ and within a segment of length x is $e^{-x/L}$. The desired distribution $f(x)$ is obtained by multiplying $e^{-1/L}$ by $1/L$ to normalize the distribution. Thus,

$$f(x) = (1/L)e^{-x/L}, \quad [6]$$

which is the well-known negative exponential distribution. The expectation of the sample mean $[E(x')]$ is given by the product of x and $S(x)$ integrated over all possible values of x and normalized (by division) by the integral of $S(x)$ over the same values,

$$E(x') = \int_0^C xS(x)dx / \int_0^C S(x)dx, \quad [7]$$

where C is the length of a typical mouse chromosome. Noting that these integrals evaluated at $x = C$ approach 0 when C is large relative to L, we obtain

$$\int_0^C xS(x)dx \cong L - 1/[L(D + L^{-1})^2] - 2D/[L(D + L^{-1})^3] \quad [8]$$

and

$$\int_0^C S(x)dx \cong 1 - 1/[L(D + L^{-1})] - D/[L(D + L^{-1})^2]. \quad [9]$$

By substituting Eqs. 8 and 9 into Eq. 7 and simplifying, we obtain

$$E(x') \cong (L^2D + 3L)/(LD + 1). \quad [10]$$

Thus, the expected sample mean $[E(x')]$ of the transformed segment lengths ($\hat{m}$) is defined by L, the mean length of conserved segments in centimorgans, and D, the density of mapped homologous loci in the genome ($D = T/G$). For data given in Fig. 1, $T = 54$, $G = 1{,}600$ cM; therefore $D = 0.0338$ loci per cM. By replacing $E(x')$ in Eq. 10 with its estimate, the mean transformed segment length (20.9 cM), we find that $L = 8.1$ cM. Thus, the average length of autosomal segments conserved since divergence of man and mouse is about 8 cM.

If we use large-sample estimation theory, the estimated variance of L is given by

$$V(L) \cong V(x')(dL/dx')^2, \quad [11]$$

where $V(x')$ is the empirical sampling variance of x'; here $V(x') = 12.6$. By differentiating Eq. 10 with respect to L, we obtain

$$dx'/dL = [(LD + 1)(2DL + 3) - (DL^2 + 3L)D]/(LD + 1)^2 \quad [12]$$

and dL/dx' is the reciprocal of dx'/dL. By substituting the

numerical values of L, D, and $V(x')$, we estimate the mean and standard error of conserved segment lengths to be 8.1 ± 1.6 cM.

We plotted (data not shown) the assumed underlying negative exponential distribution of segment lengths [$f(x)$ (Eq. 6) with $L = 8$] for comparison with the expected sample distribution of lengths [$S(x)$ (Eq. 5) with $L = 8$ and $D = 0.0338$]. Most of the 13 transformed segment lengths fell in the region of the principal density of $S(x)$. A plot of the normalized cumulative distributions of $S(x)$

$$\int_0^x S(x)dx / \int_0^\infty S(x)dx, \quad [13]$$

for $L = 4$, 8, and 12 is shown in Fig. 2. The cumulative distribution of the transformed segment lengths was plotted for comparison. The agreement was very good for $L = 8$ and appreciably worse for $L = 4$ or 12. Thus, the data appear to be consistent with the assumptions of the analysis.

PROBABILITY OF LINKAGE IN MAN

The estimate of mean conserved segment length, L, can be used to predict the probability (P) that two loci are linked in man given that the homologous mouse loci are known to be x cM apart. Thus, P is equal to the probability that there have been no rearrangements in a segment x cM long when the mean number of rearrangements per cM is $1/L$. If it is again assumed that rearrangements are distributed at random, P is given by the first term of the Poisson distribution with mean x/L,

$$P = e^{-x/L}. \quad [14]$$

For example, the mouse renin structural genes (*Rnr*) are closely linked to the peptidase-3 gene (*Pep-3*) on chromosome 1 (41). *PEPC*, the human homologue of *Pep-3*, is located on the long arm of human chromosome 1 (2). If 0.5 cM is taken as the best estimate of the distance between *Pep-3* and *Rnr* in the mouse, the probability that human renin genes are linked to *PEPC* is 0.94. Similarly, the lens γ-crystallin gene (*Len-1*) of the mouse is located approximately 5 cM from the isocitrate dehydrogenase-1 gene (*Idh-1*) on chromosome 1 (42). *IDH1*, the human homologue of *Idh-1*, is located on the short arm of human chromosome 2 (2). If 5 cM is accepted as the distance between *Len-1* and *Idh-1* in the mouse, the probability that *IDH1* and the human homologue of *Len-1* are linked in man is 0.54.

RATE OF CHROMOSOMAL EVOLUTION

Lengths of conserved segments can be used to calculate the rate at which linkage homologies are disrupted during evolution. The total number of conserved segments is equal to the total genome length, G, divided by the mean length of conserved segments, L. Because each linkage disruption increases the number of conserved segments by one, the total number of conserved segments is equal to the number of autosomes present in the last common ancestor of mouse and man (N_0) plus the number of disruptions (R) that have accumulated since divergence. Thus,

$$R = (G/L) - N_0. \quad [15]$$

The variance of R, $V(R)$, which was estimated by the same method used to estimate $V(L)$, is given by

$$V(R) = (dR/dL)^2 V(L). \quad [16]$$

By treating G and N_0 as constants in Eq. 15, we have

$$V(R) = (G^2/L^4) V(L). \quad [17]$$

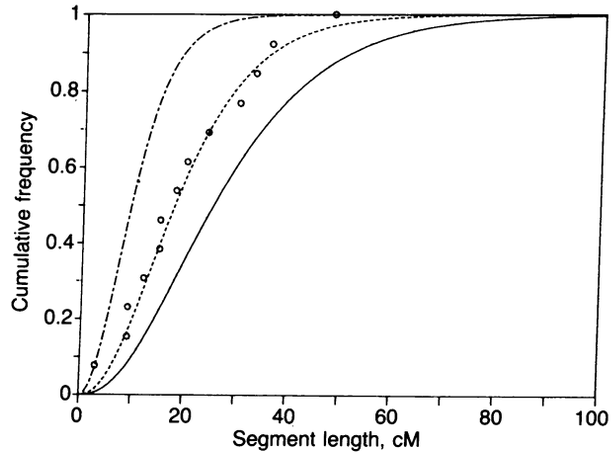

FIG. 2. Curves illustrating expected cumulative frequency distribution of segments containing two or more markers. –·–, $L = 4$ cM; ---, $L = 8$ cM; ——, $L = 12$ cM. $D = 0.0338$. The circles show the cumulative distribution of adjusted segment lengths in the sample.

For the mouse, $G = 1{,}600$ cM and $L = 8.1$ cM; N_0 is assumed to be 20 (43); therefore, $R \cong 178 \pm 39$. Thus, approximately 180 disruptions of linkage homologies have occurred since divergence of man and mouse. To calculate a rate of disruption, R was divided by twice the divergence time—i.e., $2 \times 70{,}000{,}000$ years (70 myr). This adjustment was necessary because R represents the sum of disruptions in the two lineages. The rate is approximately 1.3 disruptions per myr and is equivalent to 0.63 reciprocal translocations per myr. This slow rate is comparable with rates based on changes in chromosome number and arm number (44–46) and suggests that chromosomal rearrangements have not contributed significantly to anatomical, physiological, or behavioral differences between man and mouse. A limitation of the proposed method is that the calculations yield the sum of the disruptions in the two lineages and not the number for individual lineages. As a result, variation between lineages cannot be assessed. A method for calculating R for individual lineages will be presented elsewhere.

DISCUSSION

An important assumption made in estimating L is that when two or more pairs of homologous genes are found to be syntenic, they are presumed to occupy an uninterrupted chromosomal segment. However, inversions and transpositions can disrupt a conserved segment without affecting synteny of genes located in the interrupted segment. If one or more of the 13 mouse segments were interrupted, the length of conserved segments might be substantially overestimated. This caveat would not apply if the interruption occurred on the human chromosome or if all identified markers fall within one part of the interrupted segment. To date only one example of an interrupted segment has been identified, despite the fact that homologous loci have been mapped to 37 distinct segments. The exceptional segment is marked by *Ldh-1* and *Hbb* and is disrupted by *Idh-2*; this segment was not included in calculations for estimating L. In general, interrupted segments may not constitute a serious source of error in estimating L.

Translocations and inversions are not the only mechanisms that disrupt linkage; transposition of single loci from one chromosomal location to another also disrupts linkage. Examples of loci believed to be rearranged by transposition include a murine α-globin pseudogene (47), a human immunoglobin λ chain pseudogene (48), a human β-tubulin pseudogene (49), a human metallothionein pseudogene (50), and several human dihydrofolate reductase genes (51). Rates of

transposition are not known, however, and there is no reason to postulate that transposition explains any significant portion of the genetic rearrangements that have occurred since divergence of man and mouse. In addition, there is no evidence that transposed loci are expressed. Another mechanism of genetic rearrangement involves whole chromosome duplication and differential silencing of duplicated loci in different lineages (52). We are not aware of any evidence that this process has occurred since divergence of man and mouse. As a result, chromosomal rearrangements such as translocations and inversions appear to be the principal means of disrupting linkage during genomic evolution.

Linkage conservation has been regarded as evidence that certain autosomal segments are protected from chromosome rearrangements because of regulatory or functional interactions between the loci involved. This argument has been applied to conserved segments marked by the major histocompatibility complex and linked loci (53–56), the β-globin complex (37), and albumin and α-fetaprotein (17). The present analysis suggests that these arguments may be unnecessary. Given the infrequency of linkage disruptions since divergence of man and mouse and the apparently random distribution of these disruptions in the genome, many long chromosomal segments are expected to be conserved, regardless of the function of loci within each segment (Fig. 2). Conserved segments are probably relics of ancient linkage groups not yet disrupted by chromosome rearrangements (cf. ref. 57). As a result, evidence other than linkage conservation in a few species is required to show that particular autosomal segments have been protected from rearrangement.

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