THE ROYAL SOCIETY

A brief history of human autosomes

David Haig

Department of Organismic and Evolutionary Biology, Harvard University, 26 Oxford Street, Cambridge MA 02138, USA (dhaig@oeb.harvard.edu)

CONTENTS PAGE

1. Introduction 1448
2. Methods 1448
3. Ancestral karyotypes 1450
   (a) Common ancestor of catarrhine primates 1450
   (b) Common ancestor of extant primates 1451
   (c) Common ancestor of primates and artiodactyls 1453
   (d) Telomeric and pericentric rearrangements 1453
   (e) Stability and change 1453
4. Histories of individual human autosomes 1455
   (a) Human chromosome 1 1455
   (b) Human chromosome 2 1456
   (c) Human chromosomes 3 and 21 1458
   (d) Human chromosome 4 1458
   (e) An interlude concerning paralogy 1459
   (f) Human chromosome 5 1459
   (g) Human chromosome 6 1460
   (h) Human chromosome 7 1460
   (i) Human chromosome 8 1461
   (j) Human chromosome 9 1461
   (k) Human chromosome 10 1461
   (l) Human chromosome 11 1462
   (m) Human chromosomes 12 and 22 1462
   (n) Human chromosome 13 1463
   (o) Human chromosomes 14 and 15 1463
   (p) Human chromosome 16 1464
   (q) Human chromosome 17 1465
   (r) Human chromosome 18 1465
   (s) Human chromosome 19 1465
   (t) Human chromosome 20 1465
   (u) Marker chromosomes 1466
References 1466

Comparative gene mapping and chromosome painting permit the tentative reconstruction of ancestral karyotypes. The modern human karyotype is proposed to differ from that of the most recent common ancestor of catarrhine primates by two major rearrangements. The first was the fission of an ancestral chromosome to produce the homologues of human chromosomes 14 and 15. This fission occurred before the divergence of gibbons from humans and other apes. The second was the fusion of two ancestral chromosomes to form human chromosome 2. This fusion occurred after the divergence of humans and chimpanzees. Moving further back in time, homologues of human chromosomes 3 and 21 were formed by the fission of an ancestral linkage group that combined loci of both human chromosomes, whereas homologues of human chromosomes 12 and 22 were formed by a reciprocal translocation between two ancestral chromosomes. Both events occurred at some time after our most recent common ancestor with lemurs. Less direct evidence suggests that the short and long arms of human chromosomes 8, 16 and 19 were unlinked in this ancestor. Finally, the most recent common ancestor of primates and artiodactyls is proposed to have possessed a chromosome that combined loci from human chromosomes 4 and 8p, a chromosome that combined loci from human chromosomes 16q and 19q, and a chromosome that combined loci from human chromosomes 2p and 20.

Keywords: comparative mapping; chromosome painting; conserved synteny; ancestral karyotype; primates; artiodactyls

Received 19 October 1998 *Accepted* 26 November 1998

1. INTRODUCTION

Chromosomes do not fossilize, but ancestral chromosomal states can (at least in principle) be reconstructed from the pattern of similarities and differences of the genetic maps of extant species. My aim here is to present a set of hypotheses about the evolution of human autosomes based on the accumulated data of comparative gene mapping and comparative cytogenetics. Because less is known about the linear order of genes along chromosomes than about which genes belong on which chromosomes, my analysis will disregard inversions (which rearrange gene order within a chromosome) and emphasize reciprocal translocations, fissions and fusions (which join or fragment ancestral linkage groups). These hypotheses are provisional and will undoubtedly be modified as new data become available. Perhaps, at some time in the future, the genetic maps of extant species can be supplemented by a historical atlas of their ancestors' chromosomes.

A knowledge of ancestral karyotypes has several potential uses. First, the identification of regions of conserved synteny allows the location of a gene in one species to be predicted from the location of its homologue in another species. In this way, gene mapping in other species can be used to narrow the search for disease-associated loci in humans, and gene locations in humans can be used to identify homologues in laboratory animals that can be 'knocked-out' to develop animal models of human disease. Second, an accurate history of duplicated (paralogous) segments in the genome can help to reconstruct the evolution of multigene families. Third, chromosomal differences between species can help to resolve the species' phylogeny, but only if ancestral character states can be distinguished from derived character states. Fourth, mapping karyotypic changes to phylogenetic trees will help to elucidate the role of chromosomal rearrangements in speciation and macroevolution.

The reconstruction of ancestral karyotypes requires the repeated application of simple, mundane chains of reasoning (described in § 2). The problem of describing this process in an interesting way can be likened to the difficulty of writing an entertaining account of the piece-by-piece assembly of a jigsaw puzzle: the process is fundamentally nonlinear and ill-suited to conventional narrative. Nevertheless, it is important to lay out my evidence and arguments in some detail because the strength of evidence in support of different hypotheses varies from highly convincing to merely suggestive, and because some arguments will need to be revised if future analyses contradict my working hypothesis about the phylogenetic relationships between higher mammalian taxa. Therefore I have chosen to present my overall conclusions first (§ 3), without the full supporting evidence, followed by more detailed discussions of individual human chromosomes (§ 4). In fact, § 4 can be considered as an overgrown appendix that should be consulted for details but never read at one sitting.

2. METHODS

Two loci are said to be syntenic if they reside on the same chromosome. Conserved synteny has been defined as 'the syntenic association of two or more homologous genes in two separate species regardless of gene order or interspersing of non-contiguous asyntenic segments between the two markers' (Comparative Genome Organization; First International Workshop 1996). The further qualification should be added that synteny is conserved if and only if the shared association of markers has been inherited from the most recent common ancestor of the two species and has not subsequently been disrupted in the lineage of either species. Conserved synteny can then be contrasted with coincidental shared synteny, which occurs when markers are syntenic in two species for reasons other than uninterrupted ancestral linkage. As an example of coincidental shared synteny, *LRP2* and *IL1A* both map to human chromosome 2 and mouse chromosome 2 but there is strong evidence that these genes were unlinked as recently as the last common ancestor of humans and chimpanzees (§ 4(b)). In the language of cladistics, conserved synteny is resemblance due to symplesiomorphy, whereas coincidental shared synteny is resemblance due to homoplasy. Coincidental shared synteny, if undetected, could lead to an erroneous conclusion that two markers were ancestrally linked.

Inferences based on the shared absence of linkage are much weaker than inferences based on shared linkage. Suppose that chromosomes were assembled by randomly drawing loci from an urn without replacement. If a species had several chromosomes, many more pairs of loci would be unlinked than linked. Therefore if the random assignment of loci to linkage groups were repeated for a second species, there would be many more pairs of loci that were unlinked in both species than were linked in both. The argument is informal, but suggests that greater weight should be attached to shared linkage than shared non-linkage when reconstructing ancestral linkage groups. Put in other words, homoplasy is more likely for shared non-synteny than for shared synteny.

Linkage relationships between pairs of species are conveniently represented by an Oxford Grid in which rows represent chromosomes of one species, columns represent chromosomes of the other species, and occupied cells represent genes or chromosome segments that map to the corresponding row and column. In the absence of other evidence it is parsimonious to assume that, if two genes belong to the same cell of an Oxford Grid, the genes were linked in the common ancestor of the grid-species. Otherwise, two independent translocations would be required to explain their present linkage. However, parsimony is not an infallible guide. As the number of translocations that fragment ancestral linkage groups increases, so does the probability that some cells of a grid will contain genes that have been brought together by chance in the two species. ('Translocation' will be used in this paper as a collective term for all rearrangements that alter synteny, including reciprocal translocations, transpositions, fissions and fusions.)

An Oxford Grid can be considered to be a first-order hypothesis about linkage in the common ancestor of the grid-species. That is, members of a grid-cell are hypothesized to be linked in the common ancestor but no presumption is made about the linkage or non-linkage of loci from different cells. Hypotheses about the ancestral linkage of loci from different grid-cells can be generated by comparing linkages of more than two species if something is known about their phylogeny. For example, two cells of an Oxford Grid can be inferred to have been linked in the common ancestor of the grid-species by using information from a third, more distantly related, species (an outgroup). If a pair of loci are linked in the outgroup and one of the grid-species, then the most parsimonious explanation is that the loci were linked in

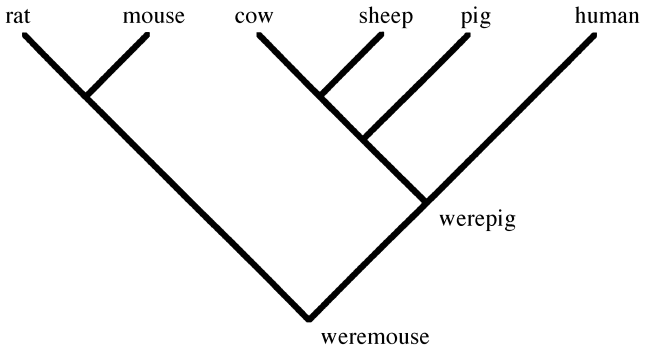

Figure 1. Putative phylogeny of the six mammalian species for which most genes have been mapped. The most recent common ancestor of primates and artiodactyls is labelled the werepig. The most recent common ancestor of rodents and primates (plus artiodactyls) is labelled the weremouse.

the common ancestor of the three species and in the (more recent) common ancestor of the grid-species.

Two principal sources of data will be used in this paper to identify occupied cells of Oxford Grids. Comparative mapping provides evidence of conserved synteny when two (or more) loci are mapped to the same chromosome in two (or more) species. Chromosome painting identifies regions of homology between two species without mapping individual loci. In this procedure, chromosome-specific 'paints' from one species are hybridized to the chromosomes of a second species (Wienberg & Stanyon 1997). Chromosome painting is an invaluable source of information about chromosomal homologies of species in which few genes have been mapped, but can fail to identify some small regions of homology.

Genetic maps are currently best known for six mammalian species: humans, mice, rats, cattle, sheep and pigs. Figure 1 presents a putative phylogeny of these species in which rodents (rats and mice) are the outgroup to artiodactyls (sheep, cattle and pigs) and primates (humans). The phylogeny is supported by the analysis by Li *et al.* (1990) of nuclear genes and that by Penny & Hasegawa (1997) of entire mitochondrial genomes. However, other molecular data support an alternative arrangement in which artiodactyls are the outgroup to rodents and primates (see, for example, Stanhope *et al.* 1996). The third possibility, that primates are the outgroup to rodents and artiodactyls, has few (if any) supporters. Many, but not all, of this paper's conclusions are robust to exchanging artiodactyls and rodents as the outgroup. The evidence seems strongest for the first interpretation (rodents as outgroup (Cao *et al.* 1998)); this will be my working hypothesis. The other features of the phylogenetic tree are uncontroversial: rats and mice are more closely related to each other than to any of the other species; and, among the artiodactyls, pigs are the outgroup to cattle and sheep (Gatesy 1997). Comparative mapping in these species allows inferences to be drawn about the linkage groups of two human ancestors, namely the most recent common ancestor of primates and artiodactyls, and the most recent common ancestor of primates (plus artiodactyls) and rodents. For want of better names, I shall call these creatures the werepig and weremouse.

Mapping data were obtained from the literature and from computer databases: the Human Genome Database (GDB) for human map locations (Letovsky *et al.* 1998); the Mouse Genome Database (MGD) for map locations in mice and homologies with other species (Blake *et al.* 1998); Bovmap (http://locus.jouy.inra.fr/cgi-bin/bovmap/Bovmap/main.pl) for cattle; SheepMap (http://dirk.invermay.cri.nz/) for sheep; PiGMaP (http://www.ri.bbsrc.ac.uk/pigmap/ecpigmap.html) for pigs; and RatMap (http://ratmap.gen.gu.se/) for rats. Homologous loci sometimes have different names, and different symbols, in different species. In such cases, I have used the human locus symbol (from GDB) to refer to all homologues. All databases contain errors and, to be conservative, I have ignored Oxford Grid cells that contain a single locus, unless there is independent evidence for the map locations. The paper has had a long gestation and has been periodically updated as new information became available, but it is possible that some bits of outdated information have survived from earlier drafts. As far as possible, however, the final version is intended to reflect the content of the public databases in mid-1998.

The chromosomes of humans, mice, rats, cattle, sheep and pigs will be distinguished by a single-letter prefix (h, m, r, c, s and p, respectively). Thus, h1 will refer to human chromosome 1, m2 to mouse chromosome 2, and so on. The cells of an Oxford Grid will be identified by the shorthand names of two chromosomes separated by a solidus (for example, h1/m4 will refer to the set of genes that map to human chromosome 1 and mouse chromosome 4). These conventions can be adapted to refer to sets of loci formed from the union of two or more grid-cells (h1/m(3 + 4) will refer to the set of loci that map to either h1/m3 or h1/m4) and to refer to genes that map to the same chromosome in three or more species (for example h7/c4/p18). There has been considerable confusion in the literature as to the numbering of cattle chromosomes. This paper adopts the standardized nomenclature of Popescu *et al.* (1996).

Table 1 lists species whose chromosomes have been hybridized with 'paints' derived from a complete set of human autosomes. With the exception of *Sorex araneus*, these species can be classified as ferungulates or primates. Ferungulates are members of a proposed clade that includes carnivores, artiodactyls and perissodactyls (Krettek *et al.* 1995; Penny & Hasegawa 1997). If ferungulates are indeed a monophyletic group, then horses, cats and pigs share the werepig as their most recent common ancestor with primates. *Tursiops truncatus* (bottlenose dolphin) is listed as an artiodactyl on the basis of recent evidence that whales are more closely related to cattle than cattle are to pigs (Shimamura *et al.* 1997). The phylogenetic affinities of *Sorex* are unclear. 'Insectivores' are traditionally considered to be an outgroup (or outgroups) of other eutherians (see, for example, Dixkens *et al.* 1998). However, two recent molecular studies place soricid insectivores closer to ferungulates than to either primates or rodents, although the authors do not place strong confidence in this placement (Onuma *et al.* 1998; Stanhope *et al.* 1998).

Strepsirrhine primates are represented in table 1 by *Eulemur fulvus mayottensis*. This lemur will serve as an outgroup to the other primates. Platyrrhine primates (New World monkeys) are the sister group to catarrhine primates. The latter are divided into two monophyletic groups: apes (including humans) and Old World monkeys (represented by *Presbytis*, *Colobus* and *Macaca*). Among the apes, our closest relative is *Pan*, followed (in order of decreasing relatedness) by *Gorilla*, *Pongo* and *Hylobates* (Purvis 1995). This paper will make frequent reference to the results of chromosome painting. For the sake of brevity, the species of table 1 will be identified simply by their generic name, but the statements might not apply to other members of the genus (*Hylobates* will be identified to species). In all cases, the source of the information can be found by consulting the references cited in table 1.

Table 1. *Species whose karyotypes have been 'painted' with a complete set of human chromosome-specific libraries*

primates	
catarrhine primates	
Pan troglodytes (chimpanzee)	Jauch *et al.* (1992)
Gorilla gorilla (gorilla)	Jauch *et al.* (1992)
Pongo pygmaeus (orang-utan)	Jauch *et al.* (1992)
Hylobates lar (lar gibbon)	Jauch *et al.* (1992)
Hylobates syndactylus (siamang)	Koehler *et al.* (1995*a*)
Hylobates concolor (concolor gibbon)	Koehler *et al.* (1995*b*)
Presbytis cristata (silvered leaf monkey)	Bigoni *et al.* (1997*a*)
Colobus guereza (black and white colobus)	Bigoni *et al.* (1997*b*)
Macaca fuscata (Japanese macaque)	Wienberg *et al.* (1992)
platyrrhine primates	
Ateles geoffroyi (black-handed spider monkey)	Morescalchi *et al.* (1997)
Alouatta seniculus (red howler monkey)	Consigliere *et al.* (1996)
Cebus capucinus (capuchin monkey)	Richard *et al.* (1996)
Callithrix jacchus (common marmoset)	Sherlock *et al.* (1996)
strepsirrhine primates	
Eulemur fulvus mayottensis	Müller *et al.* (1997)
ferungulates	
artiodactyls	
Sus scrofa (pig)	Rettenberger *et al.* (1995*a*)
	Frönicke *et al.* (1996)
	Goureau *et al.* (1996)
Bos taurus (cattle)	Hayes (1995)
	Solinas-Toldo *et al.* (1995)
	Chowdhary *et al.* (1996)
Muntiacus muntjak vaginalis (Indian muntjac)	F. Yang *et al.* (1995, 1997*a*, 1997*b*)
	Frönicke & Scherthan (1997)
Tursiops truncatus (Atlantic bottlenose dolphin)	Bielec *et al.* (1998)
carnivores	
Felis cattus (cat)	Rettenberger *et al.* (1995*b*)
	Wienberg *et al.* (1997)
Phoca vitulina (harbor seal)	Frönicke *et al.* (1997)
Mustela vison (American mink)	Hameister *et al.* (1997)
perissodactyls	
Equus caballus (horse)	Raudsepp *et al.* (1996)
insectivores	
Sorex araneus (common shrew)	Dixkens *et al.* (1998)

3. ANCESTRAL KARYOTYPES

My overall conclusions will be presented as a set of conjectures about the linkage groups of the most recent common ancestors of catarrhine primates (§ 3(a)), of all extant primates (§ 3(b)) and of primates and artiodactyls (§ 3(c)). Tentative karyotypes for these human ancestors are presented as the 'Cambridge Grids' of tables 2–4. A Cambridge Grid is simply an Oxford Grid in which cells that are proposed to have been linked in the most recent common ancestor of the grid-species are given the same identifying symbol (there is no necessary homology between chromosomes represented by the same symbol in the three Cambridge Grids, although I have tried to maintain a loose correspondence). The Cambridge Grids are based primarily on the results of chromosome painting and have undoubtedly missed some small regions of homology that have arisen because the initial fragment of translocated chromosome was small or because two (or more) larger translocations had nearby breakpoints. Therefore tables 2–4 should be considered as a framework around which more detailed reconstructions of ancestral karyotypes can be assembled.

My analysis also provides evidence about ancestral linkage groups in the most recent common ancestor of rodents and primates, but I have not attempted to construct a Cambridge Grid for this creature (the weremouse). Consideration of its karyotype is deferred to the discussions of individual human chromosomes (§ 4). In § 3(d) I discuss the instability of terminal and pericentric segments of chromosomes; in § 3(e) I discuss variation in the rate of chromosomal change, and its evolutionary significance.

(a) *Common ancestor of catarrhine primates*

Table 2 presents a Cambridge Grid for *Homo sapiens* and *Macaca fuscata* based on the chromosome-painting data of Wienberg *et al.* (1992). *M. fuscata* was chosen for this comparison, rather than *Presbytis cristata* or *Colobus*

Table 2. *Cambridge Grid representing the karyotype of the most recent common ancestor of catarrhine primates*

The autosomes of *Homo sapiens* (a representative ape) and *Macaca fuscata* (an Old World monkey) are represented, respectively, by columns 1–22 and rows 1–20. Occupied grid-cells are taken from the chromosome-painting study of Wienberg *et al*. (1992). Each autosome of the proposed ancestral karyotype ($2n = 46$) is represented by a different Greek letter. Thus, the loci of human chromosomes 14 and 15 are proposed to have been linked in the most recent common ancestor of catarrhine primates, whereas the loci of human chromosome 2 are proposed to have been divided between two separate linkage groups.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	α																					
2							η														υ	
3			δ																			
4				ϵ																		
5					ϕ																	
6						γ																
7														ο	ο							
8								ι														
9		β																				
10										κ												
11											λ											
12												μ										
13																				τ		ω
14									φ													
15		χ																				
16													ν									
17																	θ					
18																		ρ				
19																			σ			
20																π						

guereza, because the karyotype of *Macaca* has undergone fewer translocations since the common ancestor of catarrhine primates. However, similar conclusions are reached if *Presbytis* or *Colobus* is used in the place of *Macaca* (D. Haig, unpublished data).

The common ancestor of all extant catarrhine primates is proposed to have had a karyotype of 46 chromosomes in which the loci of h2 were located on two smaller chromosomes (β and χ) and the loci of h14 and h15 were linked on a single chromosome (ο). The fusion that produced h2 occurred after humans diverged from chimpanzees, but the fission of h(14 + 15) occurred before great apes diverged from gibbons. For both translocations, *M. fuscata* retains the ancestral arrangement.

The karyotypes of macaques and humans differ by two other translocations for which humans retain the ancestral state: h7 and h21 both paint macaque chromosome 2; and h20 and h22 both paint macaque chromosome 13. Chromosome painting reveals no evidence of an h(7 + 21) synteny group in *Presbytis* or *Colobus* (nor is there evidence in apes, New World monkeys, artiodactyls or carnivores). Therefore macaque chromosome 2 seems to have originated from a recent fusion in the macaque lineage. h20 and h22 also paint a single chromosome in *Alouatta*. However, chromosome painting reveals no evidence of this association in other species, including other Old World monkeys (*Presbytis*, *Colobus*) and New World monkeys (*Ateles*, *Callithrix*, *Cebus*). The simplest scenario is that loci of h20 and h22 have recently, and independently, become linked in *Macaca* and *Alouatta*.

(b) *Common ancestor of extant primates*

Table 3 presents a Cambridge Grid for *H. sapiens* and *E. fulvus mayottensis*. Chromosome painting of *Eulemur* chromosomes with human autosomal probes identified 38 occupied grid-cells (Müller *et al.* 1997). These cells can tentatively be assigned to 24 ancestral autosomes, yielding a karyotype of $2n = 50$ for the last common ancestor of

Table 3. *Cambridge Grid representing the karyotype of the most recent common ancestor of catarrhine and strepsirrhine primates*

Columns 1–22 represent the autosomes of *Homo sapiens* (a representative catarrhine). Rows 1–29 represent the autosomes of *Eulemur fulvus mayottensis* (a representative strepsirrhine). Occupied grid-cells are taken from the chromosome-painting study of Müller *et al*. (1992). *Eulemur* chromosome 29 remained unpainted by human chromosomes. Each autosome of the proposed ancestral karyotype is represented by a different Greek letter.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1			δ						φ												δ	
2	α																					
3														o	o				σ			
4		β		ϵ																		
5						γ																
6								ι							o							
7							η															
8		χ																				
9													ν									
10												μ										μ
11											λ											
12							η															
13				ϵ		γ																
14										κ												
15																	θ					
16																		ρ				
17																				τ		
18				ϵ															ξ			
19												ω										ω
20																π						
21								ζ														
22	α																					
23	α																					
24																ψ						
25					ϕ																	
26										κ												
27							η															
28					ϕ																	
29																						

extant primates. This number is provisional. *Eulemur* chromosome 29 was not painted by any of the human probes and could conceivably represent an additional ancestral linkage group. Conversely, the ancestral diploid number would decrease if future evidence were to show that some of the proposed linkage groups should be merged.

In the proposed karyotype of the ancestral primate, h2 corresponds to two chromosomes (β and χ), whereas hl4 and hl5 correspond to a single chromosome (o). These

syntenic groups are also present in the proposed karyotype of the ancestral catarrhine (§3(a)). In addition, h3 and h21 are represented by a single chromosome (δ) and the loci of h12 and h22 are shared between two ancestral chromosomes (μ and ω). The evidence for these additional rearrangements can be summarized briefly as follows.

(i) h3 and h21 both paint *Eulemur* chromosome 1. Linkage of loci from h3 and h21 has been detected in rodents, artiodactyls and platyrrhine primates, but not in catarrhine primates. Therefore *Eulemur* retains the ancestral arrangement, and h3 and h21 originated from the fission of δ after the common ancestor of platyrrhine and catarrhine primates.

(ii) h12 and h22 both paint *Eulemur* chromosome 10 and *Eulemur* chromosome 19. The arrangement in *Eulemur* is ancestral because h12 and h22 also paint shared chromosomes in ferungulates. However, h12 and h22 paint different chromosomes in catarrhine and platyrrhine primates. Therefore a reciprocal translocation has occurred between μ and ω at some time after our common ancestor with lemurs, but before the divergence of catarrhine and platyrrhine primates.

h8 and h16 both paint two chromosomes in *Eulemur*, *Callithrix*, *Cebus*, *Alouatta*, *Ateles* and ferungulates but h8 and h16 each paint a single chromosome in *Macaca*, *Colobus*, *Pongo*, *Gorilla* and *Pan*. The data are consistent with the hypothesis that h8 was formed by the fusion of ι and ζ—and h16 by fusion of π and ψ—at some time after the divergence of platyrrhine and catarrhine primates but before the divergence of apes and Old World monkeys. Similarly, h19 paints a single chromosome in (at least some species of) Old World and New World monkeys, but two chromosomes in *Eulemur* and ferungulates. Therefore a chromosomal equivalent of h19 is proposed to have been formed by fusion of σ and ξ at some time after lemurs diverged from human ancestry, but before the divergence of platyrrhine and catarrhine primates. These hypotheses are based on the absence of evidence for earlier linkage, rather than on direct positive evidence, and are thus subject to revision as better evidence becomes available.

Human chromosomes 1, 4, 5, 6, 7, 10 and 15 all paint more than one *Eulemur* chromosome, but evidence from outgroups suggests that the human linkage groups are ancestral. Human chromosomes 11, 13, 17, 18 and 20 each paint a single chromosome in *Eulemur* that is painted by no other human chromosome. Therefore these linkage groups seem to have been maintained intact in both *Eulemur* and *Homo* since their divergence from a common ancestor.

(c) *Common ancestor of primates and artiodactyls*

Table 4 presents a Cambridge Grid for *H. sapiens* and *Bos taurus*. In contrast with the previous grids, I have reordered the columns and rows to accentuate the proposed ancestral linkage groups. The grid contains 45 occupied cells assigned to 21 ancestral autosomes, yielding a karyotype of $2n = 44$ for the common ancestor of primates and artiodactyls (the werepig). This karyotype differs from that proposed for the ancestral primate by three additional translocations: a single chromosome (β) combines loci from h2p and h20 (§4(b)); a single chromosome (ϵ) combines loci from h4 and human 8p (§4(d)); and a single chromosome (π) combines loci from h16q and h19q (§4(p)). The proposals of ancestral h(2p + 20) and h(16q + 19q) linkage groups are tentative.

The modern human karyotype consists of 22 autosomal synteny sets. When compared to the proposed karyotype of the werepig (table 4), ten human autosomes (h1, h5, h6, h7, h9, h10, h11, h13, h17, h18) have gene memberships closely resembling ten ancestral autosomes. An additional six human autosomes (h3, h4, h14, h15, h20, h21) have gene memberships that have been conserved as a block since the werepig, but in these cases each ancestral synteny set also contains loci from a second human autosome (i.e. the modern synteny sets are subsets of the ancestral synteny sets). The gene memberships of the remaining human autosomes (h2, h8, h12, h16, h19, h22) are proposed to have been assembled from loci that belonged to two ancestral synteny sets. This summary refers only to 'major' changes in synteny sets, and undoubtedly overlooks some 'minor' changes that involved small chromosome segments.

(d) *Telomeric and pericentric rearrangements*

Synteny seems to be less conservative for loci at pericentric and terminal locations than for loci located in central regions of chromosome arms (Eichler 1998). Examples of recent terminal exchanges include: the translocation of the functional *IL9R* gene from an autosomal location to the human sex chromosomes (§4(p)); members of the olfactory receptor gene family that are duplicated at several subtelomeric locations (Trask *et al*. 1998); a subtelomeric domain from 17q that has spread to the terminal segments of seven other chromosomes (Monfouilloux *et al*. 1998); and the terminal segments of chromosomes 4q and 10q that are highly homologous and undergo frequent interchromosomal exchanges (Van Deutekom *et al*. 1996; Cacurri *et al*. 1998). An increased frequency of terminal translocations is not unexpected because, by definition, terminal translocations are small and are therefore less likely to have severe fitness consequences.

Examples of recent translocations to centric locations can be found on h2, h10, h16 and h19 (§§4(b), 4(k), 4(p) and 4(s)). The small h8/m16 grid-cell—{*PRKDC*, *SLUGH*, *CEBPD*}—seems to be the result of a recent translocation to 8q11 of loci that were originally located at 22q11.2 (§4(i)). The h10/m6/r4 grid-cell—{*RET*, *ALOX5*, *SDF1*}—at 10q11.2 is perhaps another example, although interpretation of this cell's history requires the mapping of its loci in additional species (§4(k)). The transposition of sequences to centric locations cannot be explained by simple reciprocal translocations and might involve novel mechanisms (Eichler *et al*. 1996; Régnier *et al*. 1997).

(e) *Stability and change*

The overriding impression from this study is the evolutionary conservatism of human synteny groups. If random pairs of syntenic loci were selected from the human genome, most would have been syntenic in the werepig. Conservatism, however, does not extend to gene order within synteny groups (Johansson *et al*. 1995; Carver & Stubbs 1997). Thus translocations seem to be evolutionarily perpetuated less frequently than inversions.

Syntenic groups are not always as stable as they seem to have been during human ancestry. A marked example

Table 4. *Cambridge Grid representing the karyotype of the most recent common ancestor of primates and artiodactyls*

The autosomes of a representative primate, *Homo sapiens*, are represented by columns; the autosomes of a representative artiodactyl, *Bos taurus*, are represented by rows. Each ancestral autosome is represented by a different Greek letter. The rows and columns have been reordered to clarify the proposed ancestral linkage groups. Occupied grid-cells are taken from the Zoo-FISH ('chromosome painting') study of Solinas-Toldo *et al.* (1995) except that (i) the numbering of cattle chromosomes 25 and 29 has been reversed to conform to the standardized nomenclature of Popescu *et al.* (1996); (ii) the h4/c24 cell of Solinas-Toldo *et al.* (1995) has been interpreted as h4/c27 (see § 4(d)); (iii) the h1/c28 cell, not detected by Solinas-Toldo *et al.* (1995), is shown as occupied because of the comparative mapping of *ACTA1* (see § 4(a)).

	1	2	20	3	21	4	8	5	6	7	9	10	11	12	22	13	14	15	16	19	17	18
2	α	χ																				
3	α																					
16	α																					
28	α											κ										
26												κ										
13			β									κ										
11		β									φ											
8							ϵ				φ											
27						ϵ	ϵ															
6						ϵ																
17						ϵ								ω	ω							
1				δ	δ																	
22				δ																		
14							ι															
7								ϕ												σ		
20								ϕ														
10								ϕ									o	o				
21																	o	o				
9									γ													
23									γ													
25										η									ψ			
4										η												
15													λ									
29													λ									
5														μ	μ							
12																ν						
18																			π	π		
19																					θ	
24																						ρ

is provided by catarrhine primates. The karyotype of *M. fuscata* differs from that of humans by as few as four major translocations (Wienberg *et al.* 1992), whereas the karyotype of *Hylobates syndactylus* (a closer human relative) differs from that of humans by at least 33 translocations (Koehler *et al.* 1995*a*). Clearly, there has been a much higher rate of chromosomal change in the gibbon lineage than in the human lineage in the time since the two

lineages diverged from their common ancestor. Rapid chromosomal change is also evident in howler monkeys, with at least 11 translocations separating the karyotypes of *Alouatta seniculus arctoidea* and *Alouatta seniculus sara* (Consigliere *et al*. 1996).

Clades undergoing rapid speciation often show chromosomal differences between closely related species, and chromosomal changes are sometimes thought to have an important role in speciation (White 1978; King 1993). However, the reconstructed history of human autosomes (presented here) is not compatible with any period of rapid chromosomal change—comparable to what is observed in gibbons or howler monkeys—having occurred at any stage in human ancestry, since we diverged from the werepig. This does not mean that theories of chromosomal speciation are necessarily wrong. Frequent chromosomal speciation could be reconciled with long-term stability of karyotypes if lineages in which there is active chromosomal change produce a large number of descendant species in the short term, but few (if any) of these species leave long-term descendants. This might be so if rapid chromosomal change is associated with costly conflicts within the genome—because of meiotic drive (Hedrick 1981) or mobile genetic elements (Wichman *et al*. 1991; Fontdevila 1992)—rather than with adaptive evolution. In the future, the reconstruction of ancestral karyotypes in multiple evolutionary lineages will provide insights about the evolutionary consequences and correlates of karyotypic stability or instability.

4. HISTORIES OF INDIVIDUAL HUMAN AUTOSOMES

Two principal kinds of evidence are used below to infer the ancestral karyotype of the werepig (represented by table 4). First, if two loci (or chromosomal segments) are linked in an artiodactyl and a primate, this is prima facie evidence that the loci were linked in the werepig. (If the ferungulates are recognized as a monophyletic group, a carnivore or a perissodactyl can be substituted for the artiodactyl of the previous sentence.) Second, if two loci are linked in a rodent and either an artiodactyl or primate, this is prima facie evidence that the loci were linked in the werepig (and the weremouse). The latter kind of inference is, of course, weaker than the former because the additional translocations that separate rodents from the werepig provide more opportunities for coincidental shared synteny.

Inferences about the karyotype of the weremouse follow the same principles but are more tenuous. If two loci are linked in a rodent and either an artiodactyl or a primate, this is prima facie evidence that the loci were linked in the weremouse. However, there is no outgroup available to determine which is the ancestral state if the loci are linked in rats and mice but are unlinked in primates and artiodactyls (or vice versa). In this case, clues might be obtained from paralogy relationships within gene families. Suppose that genes A' and A'' were derived from ancestral gene A by a *cis* duplication and that A' and A'' are linked in humans but unlinked in mice, then the parsimonious conclusion would be that the genes were linked in the weremouse. Similarly, suppose that a genetic segment AB underwent a duplication to produce segments $A'B'$ and $A''B''$; that A' and B' remain linked in humans and mice; and that A'' and B'' are linked in humans but unlinked in mice. Then the parsimonious interpretation would be that A'' and B'' were linked in the weremouse. Such forms of reasoning depend critically on being able to distinguish *cis* from *trans* duplications, because the inference will often be reversed if the duplication is misidentified, and on correctly identifying when two pairs of paralogous loci are part of the same duplication.

(a) *Human chromosome 1*

Comparative mapping reveals three large blocks of conserved synteny between human chromosome 1 and mouse chromosomes: h1/m4 (1pter→1p31), h1/m3 (1p31→1q22) and h1/m1 (1q22→1q41). Figure 2*a* presents a set of loci from h1 superimposed upon an unrooted phylogenetic tree of humans, cattle, pigs and mice. What can be inferred? First, {*ENO1*, *PGD*, *ALPL*, *FUCA1*, *LEPR*, *PGM1*} are linked in humans, mice and pigs. Therefore these loci were probably linked in the weremouse. If so, the dispersion of *ENO1*, *TSHB* and *ALPL* to three different cattle chromosomes must have occurred after the common ancestor of cattle and pigs. Second, {*CR2*, *MYOG*, *FH*} and {*ENO1*, *PGD*} are linked in humans and cattle, as are {*TSHB*, *NGFB*} and {*LEPR*, *PGM1*}. Therefore {*CR2*, *MYOG*, *FH*} and {*TSHB*, *NGFB*} were probably linked to {*ENO1*, *PGD*, *ALPL*, *FUCA1*, *LEPR*, *PGM1*} in the werepig, and in the common ancestor of cattle and pigs. If so, the dispersal of *ENO1*, *TSHB*, *MYOG* and *FH* to four pig chromosomes must have occurred after pigs diverged from cattle.

Most loci of h1 are thus conjectured to have been located on a single chromosome in the werepig and in the common ancestor of pigs and cattle. If so, this conservation is unusual. *Pan*, *Gorilla*, *Pongo*, *Macaca* and *Tursiops* are the only species from table 1 for which h1 paints a single chromosome. In contrast, h1 paints two chromosomes in *Presbytis*, *Felis*, *Phoca*, *Mustela* and *Sorex*; three chromosomes in *H. syndactylus*, *Colobus*, *Cebus*, *Callithrix*, *Eulemur*, *Equus*, *Muntiacus* and *Bos* (c2, c3, c16); four chromosomes in *Hylobates lar*, *Hylobates concolor*, *Ateles* and *Alouatta*; and five chromosomes in *Sus* (p4, p6, p9, p10, p14).

The distal long arm of human chromosome 1 (1q42→qter) contains loci that map to m8 {*RN5S*, *AGT*, *ACTA1*} and m13 {*NID*, *RYR2*, *ACTN2*}. All six loci have been mapped to p14. This suggests that h1/m8 and h1/m13 were linked in the werepig. {*ACTA1*} has been mapped to c28 in cattle (Threadgill *et al*. (1994); h1/c28 has not been detected by chromosome painting) and is therefore unlinked to most other loci from h1 in cattle, pigs and mice (figure 2*a*). One could interpret this shared absence of linkage as evidence that h1/c28/p14 was unlinked to h1/c(2 + 3 + 16)/p(4 + 6 + 9 + 10) in the werepig, but comparative mapping in *M. vison* (American mink) suggests otherwise. Figure 2*b* presents the linkage relations of selected loci from h1 and h10q superimposed on a phylogenetic tree of humans, cattle, pigs, mink and mice. Mink chromosome 2 includes {*ENO1*, *PGD*, *PGM1*} from human 1pter→1q41 and {*RN5S*} from 1q42→qter (Matveeva *et al*. 1987; Serov *et al*. 1987; Christensen *et al*. 1998). The shared linkage of these loci in humans and mink suggests that the loci were also linked in the werepig (the common ancestor of primates and ferungulates).

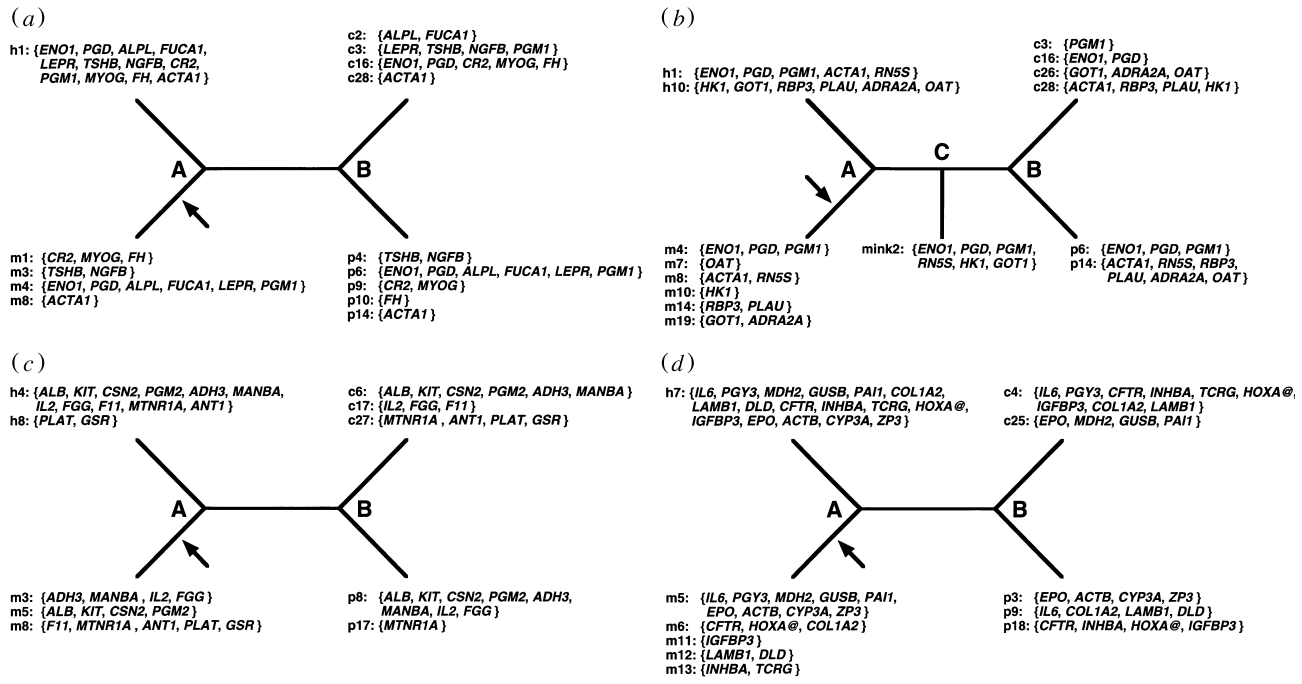

Figure 2. Comparative mapping of selected loci from mice, cattle, pigs and humans superimposed on an unrooted phylogenetic tree of the four species. The presumed root of the tree (the weremouse) is indicated by the arrow. Node A represents the most recent common ancestor of primates and artiodactyls (the werepig). Node B represents the most recent common ancestor of cattle and pigs. (*a*) Chromosome locations in mice (m1, m3, m4, m8), cattle (c2, c3, c16, c28) and pigs (p4, p6, p9, p14) of selected loci from human chromosome 1 (h1). (*b*) Chromosome locations in mice (m4, ...), cattle (c3, ...) and pigs (p6, p14) of selected loci from human chromosomes 1 and 10q. This panel also includes data from the American mink. Some data are missing (for example, *ACTA1* has not been mapped in mink; *RN5S* has not been mapped in cattle). Node C represents the most recent common ancestor of carnivores and artiodactyls. (*c*) Chromosome locations in mice (m3, m5, m8), cattle (c6, c17, c27) and pigs (p8, p17) of selected loci from human chromosomes 1 and 8p. (*d*) Chromosome locations in mice (m5, m6, m11, m12, m13), cattle (c4, c25) and pigs (p3, p9, p18) of selected loci from human chromosome 7 (h7).

The common ancestor of carnivores and artiodactyls seems to have possessed a chromosome that combined loci from h1 with loci from h10: both human chromosomes paint chromosome 2 of *Mustela*, chromosomes 10 and 14 of *Sus*, and chromosome m4 of *Phoca*. Moreover, {*ENO1*, *PGD*} from h1 and {*HK1*, *GOT1*} from h10 have been mapped to chromosome 2 of *Mustela*, and {*ACTA1*} from h1 and {*RBP3*, *PLAU*} from h10 have been mapped to p14 and c28 (figure 2*b*). These data are equivocal about whether an h(1 + 10) linkage group was present in the werepig or was formed after the divergence of primates and ferungulates. I have provisionally adopted the latter alternative because of the absence of evidence for such an association in mice. (The sporadic occurrence of a chromosome that is painted by h1 and h10 in *H. concolor*, *Colobus* and *Callithrix* seems to represent three independent translocations because h(1 + 10) was not detected in any other primate listed in table 1.)

{*CD2*, *ATP1A1*} map to h1/m3 but {*CD48*, *ATP1A2*} map to h1/m1. Therefore the *CD2*/*CD48* and *ATP1A1*/*ATP1A2* gene pairs provide evidence of an h1/m(1 + 3) syntenic block in weremouse, because this pattern would be explained if the products of an ancestral *cis* duplication were separated to different chromosomes in the rodent lineage but remained linked in humans (Y. W. Wong *et al.* 1990; Kingsmore *et al.* 1995). Whether h1/m4, h1/m8 and h1/m13 were linked to h1/m(1 + 3) in the weremouse is unclear.

(b) *Human chromosome 2*

Human chromosome 2 is the product of a recent telomere-to-telomere fusion between two acrocentric chromosomes, with the fusion point near 2q13. This fusion accounts for the difference in chromosome number between humans ($2n = 46$) and chimpanzees, gorillas and orang-utans ($2n = 48$) (Wienberg *et al.* 1994). Chromosome painting with h2 identifies two chromosomes in *Pan*, *Gorilla*, *Pongo*, *Macaca*, *Presbytis*, *Colobus*, *Alouatta*, *Cebus*, *Callithrix*, *Eulemur*, *Tursiops*, *Sus* (p3, p15), *Bos* (c2, c11), *Felis* (A3, C1), *Mustela* and *Phoca*. Clearly, the chromosomal fusion that produced h2 occurred in the human lineage after our most recent common ancestor with chimpanzees.

For purposes of discussion, the pre-fusion linkage group that contained the loci now located on 2q13→qter will be called h2a (corresponding to chromosome 13 of *Pan* and chromosome 11 of *Gorilla*) and the pre-fusion linkage group that contained the loci now located on 2pter→q13 will be called h2b (corresponding to chromosome 12 of *Pan* and *Gorilla*). Loci from h2a map to c2/p15 {*TNP1*, *LRP2*, *NEB*} and either m1 or m2, whereas loci from human 2p map to c11/p3 {*APOB*, *LHCGR*, *CD8A*} and to m6, m11, m12 or m17. In what seems a perverse coincidence, loci from proximal 2q that belong to h2b map to the same pair of mouse chromosomes (m1 and m2) as loci from distal 2q that belong to h2a.

Most loci of the h2/m1 and h2/m2 grid-cells can be assigned unambiguously to h2a. However, there is strong

Table 5. *Linkage relations of loci from h2/m1, h2/m2 and h20/m2*

The first figure in the superscript is the map location on m1 or m2 (obtained from the Mouse Genome Database). Subsequent figures in the superscript are the locations on cattle chromosomes (c2 or c11), on pig chromosomes (p15 or p17) and on cat chromosomes (catA3), when these are known. These data are used to assign loci from h2/m1 and h2/m2 to either h2a or h2b (§4(b)).

	h2a	h2b	h20
m1	COL3A1$^{21cM/c2}$	LAF4^{19cM}	—
	GDF8$^{29cM/c2/p15}$	SLC9A2^{20cM}	—
	NRAMP1$^{39cM/c2/p15}$	ZAP70^{20cM}	—
	HTR5B^{63cM}	IL1R1$^{20cM/c11}$	—
	EN1^{64cM}	IL1R2$^{20cM/c11}$	—
	INHBB$^{64cM/c2}$	ST2^{21cM}	—
	LCT$^{66cM/p15}$	NPAS2^{22cM}	—
m2	NEB$^{30cM/c2/p15}$	PAX8^{10cM}	AVP$^{73cM/c13}$
	DPP4$^{35cM/p15}$	IL1RN^{10cM}	PDYN$^{74cM/p17}$
	GCG$^{36cM/c2}$	IL1A$^{73cM/c11/p3/catA3}$	ITPA$^{74cM/c13/catA3}$
	SNC2A1$^{36cM/c2}$	IL1B$^{73cM/c11/p3}$	PRNP$^{75cM/c13}$
	LRP2$^{39cM/c2/p15}$	ADRA2B^{73cM}	CST3$^{84cM/p17}$
	GAD1$^{43cM/p15}$	BUB1^{73cM}	SRC$^{91cM/c13/catA3}$
	HOXD$^{45cM/p15}$	SLC20A1^{73cM}	ADA$^{94cM/c13/catA3}$

evidence that three members of the interleukin-1 family {*IL1A*, *IL1B*, *IL1RN*} from h2/m2 should be assigned to h2b rather than h2a and somewhat weaker evidence that three members of the interleukin-1 receptor family {*IL1R1*, *IL1R2*, *ST2*} from h2/m1 should be assigned to h2b rather than h2a. If correct, this means that the h2/m1 and h2/m2 grid-cells both contain loci that are linked in humans and mice for reasons other than uninterrupted ancestral linkage.

Table 5 summarizes linkage relationships of selected loci from h2/m1 and h2/m2, and assigns these loci to either h2a or h2b. Human *IL1A*, *IL1B* and *IL1RN* are located within 1 Mb of the interstitial telomeric repeat that is believed to represent the point of fusion between h2a and h2b (Hildebrandt *et al*. 1996). This gene cluster has been disrupted on m2, with *IL1RN* (and *PAX8*) translocated to a location more than 60 cM from *IL1A* and *IL1B*. *IL1A* and *IL1B* have been mapped to c11/p3 (together with {*APOB*, *LHCGR*, *IGK*} from human 2p) and therefore unambiguously belong to h2b. {*ADRA2B*, *BUB1*, *SLC20A1*} also map to proximal human 2q and probably belong to h2b/m2. In contrast, the loci assigned to h2a/m2 map to more distal locations on human 2q and are not interspersed with loci of h2b/m2 in either the human or mouse genome.

The evidence for assigning a subset of loci from h2/m1 to h2b rather than h2a is based solely on the mapping of *IL1R1* and *IL1R2* to c11 by multipoint linkage analysis (Yoo *et al*. 1994). This assignment should be confirmed because *IL1R1* and *IL1B* map more than 50 cM apart on c11 (Sonstegard *et al*. 1998), because loci from h2b/m1 and h2a/m1 occur close together in both the human and mouse genomes, and because the proximity of the human genes for interleukin-1 ligands and interleukin-1 receptors to each other, and to the site of the recent chromosome fusion, raises the intriguing possibility that the linkage of ligands and receptors in humans (but not in mice) was a consequence of the fusion (Haig 1996*a*).

Linkage of loci from h2a and h2b occurs in *S. araneus* as well as in humans (Dixkens *et al*. 1998). Clearly, the occurrence of an h(2a + 2b) linkage group in *Sorex* and *Homo* does not represent conserved synteny. However, it is possible that *Sorex* retains an ancestral linkage group that has been 'reconstituted' in *Homo*. If true, this scenario would help to explain the cross-membership in h2a and h2b of loci from m1 and m2. Alternatively, an h(2a + 2b) linkage group might have been absent from the common ancestor of shrews and humans, but have been derived independently in both lineages.

Table 5 hints at an ancestral association of h2b with h20: *IL1A* is located on m2 near the border of a large block of conserved synteny with h20; loci from h2b (including *IL1A*) have been mapped to chromosome A3 of cats together with loci from h20 (Wienberg *et al*. 1997); and chromosome painting reveals linkage of loci from h2 and h20 in *Phoca* and *Mustela*. On this evidence, h(2b + 20) is tentatively proposed to have been an ancestral linkage group of the werepig. If so, a similar breakpoint must have independently disrupted this linkage group in artiodactyls and primates because loci from h2b map to c11/p3, whereas loci from h20 map to c13/p17. Synteny of {*IL1A*, *IL1B*, *AK1*, *ABL1*} in cattle and mice (c11/m2)—but their separation on h2b {*IL1A*, *IL1B*} and h9 {*AK1*, *ABL1*}—probably represents coincidental shared synteny because I have found no evidence of this association in other ferungulates.

Linkage group 9 of zebrafish contains loci from h2a/m1 {*EN1*, *DES*, *IHH*} and h2a/m2 {*HOXD4*, *EVX2*, *DLX2*, *INHBB*} (Postlethwait *et al*. 1998). This suggests that these loci were linked in the common ancestor of teleost fishes and tetrapods, and that the loci of h2a/m1 and h2a/m2 were linked in the weremouse and werepig.

The neighbouring block of h2b/m6 in the mouse genome is h7/m6; the neighbouring block of h2b/m11 is h7/m11, and the neighbouring block of h2b/m12 is h7/m12. Thus, loci from h2b and h7 are closely associated on three chromosomes in mice. This association is compatible with

several possible histories. One of the simpler scenarios is that h2b/m(6 + 11 + 12) and h7/m(6 + 11 + 12) were ancestral linkage groups of the weremouse that underwent a reciprocal translocation and subsequent fissions in the rodent lineage.

Proximal h2 has undergone a number of recent rearrangements, both before and after the fusion of h2a and h2b. These changes include: sequences duplicated from Xq28 that are found near the h2 centromere in chimpanzees, gorillas and some humans, but not in orang-utans or gibbons (Eichler *et al.* 1996, 1997); a duplication of *CD8B* that is present in humans, chimpanzees and gorillas, but not orang-utans (Delarbre *et al.* 1993); a pericentric inversion that has dispersed genes of the immunoglobulin κ (*IGK*) complex to both sides of the centromere in chimps and humans, but not in gorillas (Ermert *et al.* 1995); and a duplication of *IGK* that is found on most (but not all) human chromosomes (Weichhold *et al.* 1993).

A familial pericentric inversion, inv(2)(p12q14), was detected in almost 1% of patients in an Israeli hospital and has been observed in healthy homozygotes (Gelman-Kohan *et al.* 1993). This inversion contributed 87 out of 305 independently ascertained pericentric inversions in a large French survey (Groupe de Cytogénéticiens Français 1994), and is probably the same as inv(2)(p11.2q13) that contributed 31 out of 102 familial pericentric inversions in an American survey (Daniel *et al.* (1988); neither survey included the common pericentric inversions of h9).

(c) *Human chromosomes 3 and 21*

A shared chromosome is painted by h3 and h21 in *Bos* (c1), *Sus* (p13), *Felis* (C2), *Tursiops*, *Phoca*, *Mustela*, *Tupaia*, *Oryctolagus* and *Sorex*. Among primates, h3 and h21 paint a shared chromosome in *Eulemur*, *Ateles*, *Cebus*, *Callithrix* and *Pithecia*, but different chromosomes in *Alouatta*, *Macaca*, *Presbytis*, *Colobus*, *Hylobates*, *Pongo*, *Gorilla* and *Pan* (Richard & Dutrillaux 1998; references in table 1). Thus, an ancestral h(3 + 21) linkage group seems to have been disrupted in the human lineage some time after our common ancestor with New World monkeys but before the divergence of Old World monkeys and apes (Richard *et al.* 1996; see also Threadgill *et al.* 1991; Threadgill & Womack 1991). Chromosome painting and comparative mapping suggest that the h(3 + 21) linkage group is preserved largely intact in the pig genome and, by inference, was present in the werepig.

Comparative mapping reveals traces of an ancestral h(3 + 21) association in mice and marsupials: {*PIT1*, *SIAT1*, *SST*} map to h3/c1/m16, whereas {*APP*, *SOD1*, *IFNAR1*} map to h21/c1/m16; *TF* from h3/c1/m9 and *SOD1* from h21/c1/m16 are syntenic in *Sminthopsis crassicaudata* (Maccarone *et al.* 1992). The shared synteny of {*TF*, *SOD1*} in *Bos* and *Sminthopsis*, if it is conserved synteny, would indicate that h3/m9 and h(3 + 21)/m16 were linked in the weremouse. However, the low chromosome numbers of marsupials increase the likelihood of coincidental shared synteny.

(d) *Human chromosome 4*

Chromosome painting identifies three cattle chromosomes with homology to h4. Hayes (1995) interpreted these to be R-banded chromosomes 4, 17 and 29, whereas Solinas-Toldo *et al.* (1995) interpreted them to be G-banded chromosomes 6, 17 and 24. In the nomenclature used here (Popescu *et al.* 1996), both studies identified c6 and c17, but disagreed about whether the third chromosome was c27 (the equivalent of R-banded chromosome 29) or c24. No genes have been mapped to h4/c24 but {*ANT1*, *MTNR1A*} have been mapped to h4/c27. Therefore c27 seems to be the correct identification. h4 painted a single pig chromosome (p8), but *MTNR1A* has been mapped to p17, identifying a second region of conserved synteny with h4 (Messer *et al.* 1997).

Figure 2*c* presents the linkage relations of selected loci from human chromosomes 4 and 8p. Four observations suggest hypotheses about ancestral synteny.

(i) Synteny of {*ALB*, *KIT*, *CSN2*, *PGM2*} is conserved in humans, cattle, pigs and mice. Therefore h4/c6/p8/m5 was an ancestral syntenic block in the weremouse and werepig.

(ii) Synteny of {*ADH3*, *MANBA*, *FGG*, *IL2*} is conserved in humans, pigs and mice, but not in cattle. Therefore h4/p8/m5 was a syntenic block in the weremouse, werepig and common ancestor of pigs and cattle, but the block was subsequently split between two chromosomes (c6, c17) in the cattle lineage.

(iii) Synteny of {*FI1*, *MTNR1A*, *ANT1*} is conserved in humans and mice, but not in cattle. Therefore h4/m8 was a syntenic block in the weremouse and werepig, but was split between two chromosomes (c17, c27) at some time after cattle diverged from the werepig.

(iv) Synteny of {*MTNR1A*, *ANT1*, *PLAT*, *GSR*} is conserved in cattle and mice, but not in humans. Therefore an h(4 + 8p)/m8 synteny group was present in the weremouse and werepig, but was split between two chromosomes in the human lineage.

Taken together, observations 1–4 suggest that h(4 + 8p)/c(6 + 17 + 27)/p(8 + 17)/m(3 + 5 + 8) was a syntenic block in the werepig. The hypothesis that loci from h4 and h8p were syntenic in the werepig is supported by chromosome painting: c27 is painted by h4 and h8 (see above); h4 and h8 similarly paint a shared chromosome in *Felis*, *Phoca* and *Mustela*. However, the h(4 + 8p) linkage group was disrupted at sometime before the common ancestor of extant primates, because h4 and h8 paint different chromosomes in *Eulemur*, *Ateles*, *Cebus*, *Callithrix*, *Macaca*, *Presbytis*, *Colobus*, *Pongo*, *Gorilla* and *Pan*.

Comparative mapping reveals three large blocks of conserved synteny between h4 and mouse chromosomes: h4/m5 (4pter→4q21), h4/m3 (4q21→4q31) and h4/m8 (4q31→4qter). The h4/m8 and h8/m8 cells were probably linked in the weremouse (Grewal *et al.* (1998); see also above). The h4/m3 and h4/m5 grid-cells both contain loci with paralogues on h5 (table 6; § 4(e)) and can be conjectured to have been linked in the weremouse. This is because it seems simpler to assume that the paralogies reflect a single large *trans* duplication that has been conserved intact on h4 and h5 than that the paralogies are the result of several smaller duplications that have been assembled independently on h4 and h5. The evidence is admittedly weak and subject to alternative interpretations. Curiously, several paralogies can be noted between h4/m(3 + 5) and h(4 + 8)/m8 (table 6; § 4(e)). If these paralogies were the result of a *cis* duplication or *cis*

Table 6. *Selected paralogies between human chromosomes 4, 5, 8 and 10*

Chromosomal location in the human and mouse genome (when known) is indicated by superscripts. Data obtained from the Human Genome Database (Letovsky *et al*. 1998) and the Mouse Genome Database (Blake *et al*. 1998).

h4/m(3+5)	h5	h(4+8)/m8	h10
FABP2$^{h4/m3}$	FABP6$^{h5/m11}$	—	—
FGF2$^{h4/m3}$	FGF1$^{h5/m18}$	—	—
IL2$^{h4/m3}$	IL4$^{h5/m11}$	IL15$^{h4/m8}$	—
NPY2R$^{h4/m3}$	NPY6R$^{h5/m18}$	NPY1R$^{h4/m8}$	NPY4R$^{h10/m14}$
ANX5$^{h4/m3}$	ANX6$^{h5/m11}$	—	ANX7$^{h10/m14}$
GRIA2$^{h4/m3}$	GRIA1$^{h5/m11}$	—	—
GLRB$^{h4/m3}$	GLRA1$^{h5/m11}$	GLRA3$^{h4/m8}$	—
GABRA2$^{h4/m5}$	GABRA1$^{h5/m11}$	—	—
ADRA2C$^{h4/m5}$	ADRA1B$^{h5/m11}$	ADRA1C^{h8}	ADRA2A$^{h10/m19}$
—	ADRB2$^{h5/m18}$	ADRB3$^{h8/m8}$	ADRB1$^{h10/m19}$
DRD5$^{h4/m5}$	DRD1$^{h5/m13}$	—	—
KDR$^{h4/m5}$	FLT4$^{h5/m11}$	—	—
KIT$^{h4/m5}$	FMS$^{h5/m18}$	—	—
PDGFRA$^{h4/m5}$	PDGFRB$^{h5/m18}$	PDGFRL^{h8}	—
FGFR3$^{h4/m5}$	FGFR4$^{h5/m13}$	FGFR1$^{h8/m8}$	FGFR2$^{h10/m7}$
PPP3CA^{h4}	—	PPP3CC^{h8}	PPP3CB^{h10}
GPRK2L$^{h4/m5}$	GPRK6^{h5}	—	GPRK5^{h10}
PDE6B$^{h4/m5}$	PDE6A$^{h5/m18}$	—	PDE6C$^{h10/m7}$
—	GRL$^{h5/m18}$	MLR$^{h4/m8}$	—
—	F12^{h5}	PLAT$^{h8/m8}$	PLAU$^{h10/m14}$
—	—	EIF4EB1$^{h8/m8}$	EIF4EB2$^{h10/m10}$
—	—	SLC18A1$^{h8/m8}$	SLC18A2$^{h10/m19}$

duplications, h4/m(3 + 5) and h(4 + 8)/m8 might have been ancestrally linked in the weremouse. Alternatively, the paralogies could represent the results of a *trans* duplication (or duplications) whose products were brought together at some stage in the ancestry of the werepig.

(e) *An interlude concerning paralogy*

Lundin (1993) observed that several loci from h4 could each be paired with a paralogous locus on h5. He suggested that these relationships were vestiges of an ancient doubling of the vertebrate genome. Some of these loci also have paralogues on human 8p and h10 (Pébusque *et al*. 1998). The first two columns of table 6 present an updated, and selected, list of paralogies between h4 and h5, the third column presents paralogous loci from h(4 + 8)/m8 (§4(d)), and the fourth column presents loci from h10 that have paralogues in the other columns. Loci of the first column occur on a single human chromosome but on two mouse chromosomes, whereas loci of the third column occur on a single mouse chromosome but two human chromosomes. Therefore the possibility of extended paralogy between h4/m(3 + 5) and h(4 + 8)/m8 would not have been recognized by considering linkage relationships in either mice or humans alone. Moreover, a simple list of loci from h4 with paralogues on h5 (see, for example, Lundin 1993) would include loci belonging to two distinct blocks of extended paralogy.

The recognition of large ancestral duplications (extended paralogy) is still largely impressionistic and subject to the human proclivity for finding patterns, even where no pattern exists. A minimum of two duplications are required to explain the relationships of table 6. At the other extreme, 36 duplications would be required if each paralogue were the result of an independent duplication (the number would actually be higher to take account of paralogues on other chromosomes). There is currently no fully reliable method to distinguish the products of a single large ancestral duplication from the products of multiple smaller duplications, but the reconstruction of ancient linkage groups will clearly help to distinguish recent juxtapositions of loci from conserved ancestral syntenies.

(f) *Human chromosome 5*

Chromosome painting with h5 identifies a single chromosome in *Felis*, *Phoca*, *Mustela*, *Tursiops*, *Cebus*, *Callithrix*, *Macaca*, *Colobus*, *Pan*, *Gorilla* and *Pongo*; two chromosomes in *Sorex*, *Equus* and *Sus* (p2, p16); and three chromosomes in *Bos* (c7, c10, c20). h5/c(7 + 10 + 20) probably formed an ancestral linkage group in the werepig because {*HTR1A*, *HEXB*, *MAP1B*, *HMGCR*, *RASA*} map to h5/m13 but are scattered on three cattle chromosomes: {*HTR1A*, *HEXB*, *MAP1B*} on c20, {*HMGCR*} on c10, and {*RASA*} on c7.

Most loci from h5 that have been mapped in mice are located on one of m11, m13, m15 or m18. The h5/m13 and h5/m15 cells seem to have been linked in the most recent common ancestor of rats and mice because {*PDE4D*, *HTR1A*, *DHFR*} map to h5/m13/r2, whereas {*MPLVI2*, *GHR*, *PRLR*} map to h5/m15/r2 (Qiu *et al*. 1997). The h5/m11 and h5/m18 cells also seem to have been linked to h5/m13 in the weremouse, because loci from all three cells have putative paralogues on h4 (table 6; §4(e)). The existence of an ancestral h5/m(11 + 13 + 15 + 18) linkage group in the weremouse is supported by paralogous relationships within h5 that can be explained by a series of *cis* duplications: {*IL3*, *IL4*, *IL5*, *IL13*, *CSF2*} map to h5/m11, whereas {*IL9*} maps to h5/m13;

{*PDGFRB*, *FMS*} map to h5/ml8 whereas {*FLT4*} maps to h5/ml1 (Rousset *et al.* 1995). The small h5/ml7 grid-cell can probably be added to this ancestral linkage group because *CHD1* (from h5/ml7) is linked to *GHR* (from h5/ml5) on the Z chromosome of chickens (Fridolfsson *et al.* 1998). If so, the common ancestor of rats and mice probably possessed an h5/m(11 + 17) syntenic group that was disrupted in the mouse lineage as a result of the same event that disrupted h16/m(11 + 17)/r10 (§4(p)).

(g) *Human chromosome 6*

Chromosome painting with h6 identifies a single chromosome that is painted by no other human chromosome in *Felis*, *Mustela*, *Phoca*, *Cebus*, *Callithrix*, *Macaca*, *Pongo*, *Gorilla* and *Pan*. h6 thus seems to represent an ancient syntenic group that has been conserved intact in (at least some) primates and carnivores since their most recent common ancestor. In domestic artiodactyls, h6 paints two cattle chromosomes (c9, c23) and two pig chromosomes (p1, p7). {*IGF2R*, *SOD2*} map to h6/c9/ml7, whereas {*MHC@*, *TCP1*} map to h6/c23/ml7. Therefore the most parsimonious interpretation is that h6/c(9 + 23)/p(1 + 7) was an ancestral linkage group of the werepig.

Loci from h6 map to at least six mouse chromosomes (m1, m4, m9, m10, m13, m17). At least some, and perhaps all, of these grid-cells were linked in the weremouse.

(i) Butyrophilin (*BTN*) is a chimaeric protein with carboxy-terminal sequences that resemble the *ret* finger protein (*RFP*) and amino-terminal sequences that resemble the myelin oligodendrocyte glycoprotein (*MOG*). {*BTN*, *RFP*, *MOG*} map to 6p22–p21.3 in the class I region of the human major histocompatibility complex (Vernet *et al.* 1993), but {*Rfp*, *Btn*} are located on m13 unlinked to {*Mog*} on m17 (Amadou *et al.* 1995). Therefore h6/m13 and h6/m17 were most probably linked in the weremouse.

(ii) {*ESR1*, *MYB*} map to h6/m10/r1, whereas {*MAS1*, *TCP1*, *IGF2R*} map to h6/m17/r1. Similarly, {*FYN*} maps to h6/m10/r20, whereas {*MHC@*, *GLO1*, *PIM1*} map to h6/m17/r20 (Johansson *et al.* 1998). In both comparisons, loci that are linked in rats and humans are divided between m10 and m17. These results suggest that h6/m(10 + 17)/r(1 + 20) was a syntenic block in the weremouse.

(iii) The FACIT collagens {*COL9A1*, *COL12A*, *COL19A1*} are clustered at human 6q12–q13 (Gerecke *et al.* 1997), but {*Col9a1*, *Col19a1*} map to m1 (Warman *et al.* 1993; Khaledduzzaman *et al.* 1997) unlinked to {*Col12a1*} on m9 (Oh *et al.* 1992). If these genes arose by *cis* duplications of an ancestral locus, then h6/m(1 + 9) was probably a syntenic block in the weremouse.

(iv) {*CD24*} maps to h6/m10/r8 (Johansson *et al.* 1998), whereas {*GSTA1*, *HTR1B*, *ME1*} map to h6/m9/r8. Therefore h6/m9 and h6/m10 might have been linked in the weremouse. However, this hypothesis is based on evidence from a single locus {*CD24*} and is therefore only weakly supported.

Observations (i) and (ii) argue that h6/m(10 + 13 + 17) was a syntenic block in the weremouse (and in the common ancestor of rats and mice). Observation (iv) hints that this syntenic block also included h6/m(1 + 9). Whether it also included h6/m4 is unclear.

(h) *Human chromosome 7*

Two cattle chromosomes (c4, c25) and two pig chromosomes (p9, p18) are painted by h7. (The smaller bovine chromosome painted by h7 was identified as c25 by inference from map locations listed in Bovmap). In addition, {*EPO*, *ACTB*, *CYP3A*, *ZP3*} have been mapped to h7/p3, identifying a third block of pig–human synteny that was not detected by chromosome painting (Bruch *et al.* 1996; Liu *et al.* 1998; Thomsen *et al.* 1998). Figure 2*d* presents comparative mapping data for selected loci from human chromosome 7. These data suggest the following conclusions.

(i) Synteny of {*IL6*, *PGY3*, *MDH2*, *GUSB*, *PAI1*, *EPO*} is conserved in humans and mice (h7/m5), but not in cattle. Therefore the h7/c4 and h7/c25 grid-cells were separated at some time in the ancestry of cattle, after the werepig.

(ii) Synteny of {*IL6*, *CFTR*, *INHBA*, *HOXA@*, *COL1A2*, *LAMB1*} is conserved in humans and cattle, but not in pigs. Therefore these loci belonged to a shared linkage group in the werepig, and in the common ancestor of cattle and pigs, with h7/p9 and h7/p18 becoming separated after pigs diverged from cattle.

(iii) {*IL6*} is linked to {*EPO*, *ACTB*, *CYP3A*, *ZP3*} in humans and mice, but not in pigs. Therefore h7/p3 and h7/p9 were linked in the werepig.

Observations (i)–(iii) imply that h7/c(4 + 25)/p(3 + 9 + 18) was an ancestral syntenic block of the werepig. Therefore h7 seems to be an ancient linkage group that has been conserved largely intact since the common ancestor of primates and artiodactyls. This conclusion is supported by the observation that h7 paints a single chromosome in *Equus*, *Felis*, *Phoca*, *Cebus*, *Callithrix*, *Macaca*, *Presbytis*, *Colobus* and the great apes. Despite this conservation of gene content, gene order has undergone recent rearrangement because comparative cytogenetics suggests that at least two inversions of h7—one pericentric and the other paracentric—have occurred in the human lineage since we diverged from our common ancestor with orang-utans (Borowik 1995). The pericentric inversion might explain why loci from p9 and p18, and loci from m5, m6 and m12, map to both arms of h7.

Loci from h7 map to at least five mouse chromosomes (m5, m6, m11, m12, m13) and four rat chromosomes (r4, r12, r14, r17), as follows.

(iv) {*IL6*, *PGY*, *HGF*, *NOS3*} map to h7/m5/r4, whereas {*TCRB*, *HOX@*, *MET*, *CFTR*} map to h7/m6/r4. Therefore h7/m(5 + 6)/r4 was probably a syntenic block in the common ancestor of rats and mice.

(v) *ACTB* from h7/m5 and *EGFR* from h7/m11 both map to chicken chromosome 2 (Burt *et al.* 1995). This suggests that h7/m(5 + 11) was a syntenic block in the weremouse.

(vi) *SP1*, *SP2*, *SP3* and *SP4* are each syntenic with a *HOX* cluster in the human genome, but *SP4* (h7/m12/r6) and *HOXA@* (h7/m6/r4) are unlinked in rats and mice. This suggests that h7/m(6 + 12)/r(4 + 6) was a syntenic block in the weremouse (Scohy *et al.* 1998).

Taken together, observations (iv)–(vi) suggest that h7/m(5 + 6 + 11 + 12) was a syntenic block in the weremouse. Whether this linkage group also included h7/m13 is unclear.

(i) *Human chromosome 8*

Human chromosome 8 paints a single chromosome in great apes (*Pan*, *Pongo*, *Gorilla*) and Old World monkeys (*Macaca*, *Presbytis*, *Colobus*); two chromosomes in *Cebus*, *Callithrix*, *Alouatta*, *Ateles*, *Eulemur*, *Sorex*, *Felis*, *Phoca*, *Mustela* and *Sus* (p4, p14); and three chromosomes in *Bos* (c8, c14, c27). Human 8p is painted by p14 and cat chromosome B1, whereas 8q is painted by p4 and cat chromosome F2 (Goureau *et al.* 1996; Wienberg *et al.* 1997). Moreover, loci of human 8p map to m8 and m14, whereas loci of human 8q map to m3, m4 and m15. Therefore the h8 linkage group probably came into existence by the fusion of '8p' and '8q' sometime after the last common ancestor of Old World monkeys and New World monkeys but before the last common ancestor of the Old World monkeys and apes. In § 4d, loci of human 8p were proposed to have been linked to loci from h4 in the werepig (see figure 2*c*).

The limited evidence from comparative mapping suggests that h8/c8 {*LPL*, *CTSB*, *NEFL*}, h8/c27 {*PLAT*, *GSR*} and h8/p14 {*LPL*} will contain loci from human 8p, whereas h8/c14 {*MOS*, *CRH*, *MYC*, *ODF1*} and h8/p4 {*ODF1*} will contain loci from human 8q. If so, the dispersion of loci from human 8p to c8 and c27 seems to have occurred since the last common ancestor of pigs and cattle, because p14 paints the whole of human 8p (Goureau *et al.* 1996). The mapping of {*LPL*} from h8/c8 and {*PLAT*, *GSR*} from h8/c27 to the same mouse chromosome (m8) supports the hypothesis that these grid-cells were syntenic in the werepig.

The earlier history of h8p and h8q is unclear. Human chromosome 8p and chromosome 13 both contain loci from m8 and m14. This could be interpreted as evidence for an ancestral association of h8p and h13, or as evidence for a translocation that occurred in the mouse lineage after it diverged from the weremouse. {*CA2*, *CALB1*, *MYC*} map to human 8q and chicken chromosome 2, but to three different mouse chromosomes: *CA2* on m3, *CALB1* on m4, and *MYC* on m15 (Burt *et al.* 1995). If the shared linkage of these loci in humans and chickens reflects conserved synteny, then h8q/m(3 + 4 + 15) was an ancestral linkage group of the weremouse.

{*SLUGH*, *CEBPD*, *PRKDC*} identify a small region of homology between human 8q11 and m16. In the mouse, these loci map close to *Igl@* (h22/c17/p14/r11/m16). This grid-cell might correspond to a recent translocation of material from 'h22' to 'h8' because a Vλ orphon maps to 8q11.2 (Frippiat *et al.* 1997). This orphon has more than 90% sequence identity to Vλ8a from *IGL@* at 22q11.2.

(j) *Human chromosome 9*

Chromosome painting with h9 identifies a single chromosome in *Sorex*, *Tursiops*, *Sus* (p1), *Felis*, *Mustela*, *Eulemur*, *Cebus*, *Callithrix*, *Ateles*, *Alouatta*, *Macaca*, *Colobus*, *Presbytis* and the great apes, but two chromosomes in *Bos* (c8, c11). {*IFNB1*} maps to h9/c8/p1, whereas {*GGTA1*, *HSPA5*} map to h9/c11/p1. Similarly, {*C5*, *GSN*} map to h9/c8/m2, whereas {*GGTA1*, *HSPA5*, *AK1*, *ABL1*} map to h9/c11/m2. Both lines of evidence suggest that h9/c(8 + 11) was a syntenic group of the werepig and that h9 has been conserved largely intact since this ancestor.

Loci from h9 map to at least four mouse chromosomes (m2, m4, m13, m19). Several genes of the lipocalin family map to h9 but are shared between m2 and m4: {*LCN2*, *C8G*, *PTGDS*} from h9/m2, and {*ORM1*, *AMBP*} from h9/m4 (Chan *et al.* 1994). This pattern is compatible with repeated *cis* duplications of an ancestral lipocalin gene followed by a translocation in the mouse lineage that split the gene cluster. Similar evidence for an h9/m(2 + 4) linkage group comes from the mapping of *ABC1* to h9/m4 and *ABC2* to h9/m2 (Luciani *et al.* 1994). The history of the h9/m13 and h9/m19 cells is obscure.

The homologue of h9 is acrocentric in orang-utans and gorillas, but metacentric in humans and chimpanzees, owing to a pericentric inversion in the human–chimpanzee lineage (Yunis & Prakash 1982; Tanabe *et al.* 1996). The h9 homologue is smaller than the homologues of h10, h11 and h12 in macaques, orang-utans, gorillas and chimpanzees (if size can be judged from the numbering of chromosomes). This reordering of relative chromosome size is caused by the acquisition of a large band of heterochromatin at proximal 9q in humans (Gosden *et al.* 1977).

Structural variants of chromosome 9 are the most common, cytogenetically recognizable, chromosomal variants of humans. A pericentric inversion, inv(9)(p11;q13), was detected in 0.9% of live births in Scottish hospitals (Buckton *et al.* 1980) and in 2.0% of prenatal diagnoses from New York City (Hsu *et al.* 1987). In the latter study, the frequency of the inversion was 3.6% among Blacks, but 0.7% among Whites. Individuals have been reported who are homozygous for this inversion (Wahrman *et al.* 1972; Vine *et al.* 1976). In the Scottish study, a further 0.3% of live-born infants were heterozygous for an extra large block of heterochromatin (9qh+). Variants of chromosome 9 have also been reported with additional euchromatic bands (Jalal *et al.* 1990; Reddy 1996).

(k) *Human chromosome 10*

Human chromosome 10 paints a single chromosome in *Pan*, *Pongo*, *Gorilla*, *Macaca* and *Presbytis*. This suggests that an equivalent of h10 was present in our common ancestor with Old World monkeys. h10 also paints a single chromosome in *Felis* (D2) and *Tursiops*. In contrast, h10 paints two (or three) chromosomes in *Colobus*, *Ateles*, *Alouatta*, *Cebus*, *Callithrix*, *Eulemur*, *Sorex*, *Phoca*, *Mustela*, *Equus*, *Bos* (c13, c26, c28) and *Sus* (p10, p14). These data are equivocal between two interpretations: either h10 is an ancestral linkage group that has been conserved largely intact in Old World monkeys and *Felis* but has been independently disrupted in lemurs, New World monkeys and artiodactyls, or the similarity in gene membership between human chromosome 10 and cat chromosome D2 is an example of convergence. On the basis of the principle that coincidental shared synteny is less likely than coincidental shared non-synteny, table 4 interprets h10 as an ancestral linkage group that has been conserved since the werepig.

Loci of h10p map to two mouse chromosomes (m2, m18). The mapping of *GAD2* to h10/m2/r17 and *TPL2* to h10/m18/r17 provides a hint that the h10/m2

and h10/m18 grid-cells were linked in the weremouse. If so, h10p can be conjectured to be a block of conserved synteny, inherited from the weremouse. At the time of writing, the only loci from h10p that had been mapped in artiodactyls were *IL2RA* (c13/s13) and *VIM* (c13/p10). Both loci map to h10/c13/m2 and are thus linked in cattle and mice to {*PRNP*, *ITPA*, *AVP*, *ADA*} from h20/c13/m2. This could be interpreted as evidence for an ancestral h(10 + 20)/c13/m2 linkage group in the weremouse and werepig. However, loci from h10/c13 map to proximal m2, loci from h20/c13 map to distal m2, and chromosome painting reveals no association between loci from h10 and h20 in primates, carnivores, pigs or horses. Therefore c13/m2 probably provides another example of coincidental shared synteny.

The bulk of h10q can similarly be conjectured to be a block of ancient synteny that has been conserved intact in the human lineage since at least the weremouse but has been fragmented in the mouse lineage. Figure 2*b* presents strong evidence that the h10/c26 and h10/c28 grid-cells were linked in the werepig: both cells contain loci that map to h10, p14 and mink chromosome 2. This linkage block contained loci that are dispersed on m7, m10, m14 and m19 (figure 2*b*). § 4(a) presents evidence that loci of h1 and h10q were linked in an ancestral ferungulate.

Human 10q shares loci with at least five mouse chromosomes (m6, m7, m10, m14, m19). I have found few clues about the history of h10/m6 {*RET*, *ALOX5*, *SDF1*}, but the remaining grid-cells seem to have formed a syntenic block in the weremouse. {*CYP2E*, *FGFR2*} from h10/m7 and {*GOT1*, *CYP17*, *ADRA2A*} from h10/m19 map to r1, suggesting that these cells were linked in the most recent common ancestor of rats and mice. h10/m10 can be tentatively added to the 'h10q' linkage group of the weremouse because *HK1* (h10/m10) and *PLAU* (h10/m14) both map to chromosome 1 of the tammar wallaby (Spurdle *et al.* 1997). Finally, m14 and m19 are related to each other by a series of paralogous gene pairs: {*Mbl1*, *Rbp3*, *Il3ra*} on m14, and {*Mbl2*, *Rbp4*, *Csf2ra*} on m19. In humans, {*MBL*, *MBL1P1*, *RBP3*, *RBP4*} map to 10q (Guo *et al.* 1998), whereas {*CSF2RA*, *IL3RA*} are closely linked at the Xp/Yp pseudoautosomal region (Milatovitch *et al.* 1993). This pattern is most simply explained by one or more *cis* duplications that have been split between m14 and m19 in the mouse lineage. (*CSF2RA* has been mapped to the X chromosome of sheep (Toder *et al.* 1997) and to chromosome 5 of the tammar wallaby, a marsupial autosome that contains several loci that map to eutherian X chromosomes (Gläser *et al.* 1998). Therefore {*CSF2RA*, *IL3RA*} were probably pseudoautosomal in the weremouse, with a subsequent translocation to an autosome during mouse ancestry.)

The recent history of pericentric h10 seems to have been cytogenetically unstable: duplicate clusters of zinc-finger genes occur on both sides of the h10 centromere (Jackson *et al.* 1996), and a portion of the *ALD* gene from Xq28 is inserted at 10p11 (Eichler *et al.* 1997). A familial pericentric inversion without detectable phenotype, inv(10)(p11.2q21.2), has been repeatedly ascertained in many unrelated families (Daniel *et al.* 1988; Groupe de Cytogénéticiens Français 1994; Collinson *et al.* 1997).

(l) *Human chromosome 11*

Human chromosome 11 paints two chromosomes in *Bos* (c15, c29), *Sus* (p2, p9) and *Sorex*, but a single chromosome in *Felis*, *Mustela*, *Phoca*, *Tursiops*, *Equus*, *Eulemur*, *Ateles*, *Cebus*, *Callithrix*, *Macaca*, *Presbytis*, *Colobus* and the great apes. Data in the Mouse Genome Database suggest that most, if not all, of h11 is conserved on chromosome D4 of cats {*HRAS*, *LDHA*, *FGF3*, *HBBC*, *ACP2*, *CD3*, *ETS1*, *GANAB*, *THY1*} and chromosome 1 of rabbits {*HRAS*, *LDHA*, *PTH*, *HBBC*, *ACP2*, *CD3*, *ETS1*, *APOA1*, *HPX*}. Loci from h11/r1/m7 are found on both c15 {*HBBC*, *PTH*} and c29 {*IGF2*, *LDHA*, *TYR*}. Therefore h11/c15 and h11/c29 were probably linked in the werepig. If so, the homologue of h11 has undergone independent fissions in the cattle and pig lineages because loci from h11/p2 are found on both c15 {*PTH*, *MYOD1*, *FSHB*} and c29 {*LDHA*}, and loci from h11/c29 are found on both p2 {*LDHA*} and p9 {*TYR*}. Therefore h11 seems to have been an ancestral linkage group, present in the werepig, that has been conserved intact in the human lineage.

Loci from h11 map to at least four mouse chromosomes (m2, m7, m9, m19). The h11/m7 and h11/m19 cells were probably linked in the common ancestor of rats and mice (and, by the same inference, in the weremouse) because both cells contain loci that map to r1: {*HRAS*, *TYR*, *IGF2*, *HBB*} from h11/r1/m7, and {*GSTP1*, *PYGM*} from h11/r1/m19. There is circumstantial evidence that the h11/m2 and h11/m9 cells were linked to h11/m(7 + 19) in the weremouse, because *HBB* (h11/m7) and *CAT* (h11/m2) are syntenic in tammar wallabies (Sinclair & Graves 1991). Similarly, *HBB* (h11/m7) and *PGR* (h11/m9) are syntenic in chickens (Burt *et al.* 1995). This hypothesis receives indirect support from the observation that loci from h11 and h15 map close to each other on m2, m7 and m9 (Elliott 1996). One possible interpretation is that h11/m(2 + 7 + 9 + 19) formed an ancestral linkage group that underwent a fusion or reciprocal translocation with h15/m(2 + 7 + 9) in the rodent lineage.

(m) *Human chromosomes 12 and 22*

Human chromosome 12 can be divided into two blocks with different histories. The larger block (h12a) extends from the 12p telomere to the neighbourhood of 12q23 (near *IGF1*). Loci from h12a map to c5 in cattle, p5 in pigs, and m6, m10 or m15 in mice. Loci from the smaller block (h12b) map to distal 12q in humans, c17 in cattle, p14 in pigs, and m5 in mice.

An h12a/c5/p5/m(6 + 10 + 15) syntenic block seems to have been conserved intact in the human and artiodactyl lineages, at least since the weremouse, but to have been split between three chromosomes in the mouse lineage. One of these splits occurred after the common ancestor of rats and mice because h12a/r7 unites loci that map to h12a/m10 {*IGF1*, *PAH*, *PEPB*} and h12a/m15 {*RARG*, *HOXC*, *WNT1*}. The h12a/m6 and h12a/m10 cells can be inferred to have been linked in the weremouse on the basis of paralogy between h11 and h12a (Haig 1996*b*; Patton *et al.* 1998): {*LDHB*, *KRAS2*, *PTHLH*} from h12a/m6 and {*MYF5*, *PAH*, *IGF1*} from h12a/m10 have paralogues {*LDHA*, *HRAS1*, *PTH*, *MYOD1*, *TH*, *IGF2*} on h11. These relationships are more parsimoniously explained by a single large duplication than by two (or more) smaller duplications that were fortuitously assembled on h12a. The conclusion that h12/m(6 + 10) was an ancestral

linkage group of the weremouse is supported by the mapping of {*GAPD*, *CCND2*} from h12/m6 and {*IGF1*, *LYZ*} from h12/m10 to the same linkage group in chickens (Burt *et al*. 1995; Klein *et al*. 1996; Masabanda *et al*. 1998).

Human chromosome 22 can similarly be divided into two blocks: one block (h22a) contains loci that map to c5 in cattle, p5 in pigs, and m6, m10 or m15 in mice; the other (h22b) contains loci that map to c17 in cattle, p14 in pigs, and m5, m11 or m16 in mice. Thus, loci of h12a and h22a are associated together in cattle, pigs and mice, as are loci of h12b and h22b. These relationships are most easily explained if h12 and h22 are related to c5/p5/m(6 + 10 + 15) and c17/p14/m(5 + 11 + 16) by a reciprocal translocation that occurred in the human lineage at some time after it diverged from the werepig.

Chromosome painting provides strong evidence for this translocation: h12 and h22 both paint c5 and c17 of *Bos*; p5 and p14 of *Sus*; chromosome B4 of *Felis*; chromosomes 3 and 12 of *Mustela*; chromosome m3 of *Phoca*; chromosomes 8 and 9 of *Tursiops*; chromosomes 1, 8 and 26 of *Equus*; and (most significantly) chromosomes 10 and 19 of *Eulemur*. In contrast, h12 and h22 paint different chromosomes in *Ateles*, *Alouatta*, *Cebus*, *Callithrix*, *Macaca*, *Presbytis*, *Colobus* and the great apes. Therefore a reciprocal translocation between h(12a + 22a) and h(12b + 22b) seems to have occurred sometime after our divergence from lemurs but before our divergence from New World monkeys.

A possible relict of this translocation is the presence in the human genome of *VWF* at 12p13 and an unprocessed pseudogene *VWFP* at 22q11 (Mancuso *et al*. 1991). However, the pseudogene's location might be coincidental because the evolutionary breakpoint that separates loci of h12a and h12b is located on distal 12q far from *VWF*. *VWFP* belongs to the small h22/m6 grid-cell that also contains *ATP6E* and *BID* (Footz *et al*. 1998). An alternative interpretation would be that these loci have been translocated to 'h22' from 'h12' at some time after the reciprocal translocation.

The h(12a + 22a) linkage group of the werepig was probably inherited intact from the weremouse because h12a seems to have been conserved since the weremouse (see above) and because of the close juxtaposition on m10 and m15 of loci that map to h12a and h22a. The evidence is less clear for the h(12b + 22b) linkage group. The loci of h12b/m5 and h22b/m5 were almost certainly linked in the weremouse but there is no strong evidence to suggest that this block was associated with loci from h22b/m11 or h22b/m16. One hint of an ancestral association is the observation that h(12b + 22b)/m5 and h22b/m11 are neighboured in the mouse genome by h7/m5 and h7/m11, respectively.

(n) *Human chromosome 13*

Human chromosome 13 paints a single chromosome in *Sorex*, *Bos* (c12), *Sus* (p11), *Mustela*, *Felis*, *Phoca*, *Tursiops*, *Equus*, *Eulemur*, *Ateles*, *Alouatta*, *Cebus*, *Macaca*, *Presbytis*, *Colobus* and the great apes. No other human chromosome paints c12 or p11, and no genes on h13 have been mapped to other pig or cattle chromosomes. Therefore this linkage group seems to have been conserved intact in all these species since they diverged from the werepig. Loci of the h13/c12/p11 linkage group map to m1, m5, m8 or m14. I have found no clear signal to indicate whether the h13/c12/p11/m(1 + 5 + 8 + 14) linkage group of the werepig was also present in the weremouse—and was fragmented during rodent evolution—or whether the linkage group was formed by the coalescence of unlinked fragments present in the weremouse.

(o) *Human chromosomes 14 and 15*

Human chromosomes 14 and 15 both paint c10 and c21 in cattle, and p1 and p7 in pigs. This relationship would be explained most simply by a reciprocal translocation. However, other evidence argues strongly that genes on h14 and h15 formed a single linkage group in the werepig and have been partitioned independently to two chromosomes in humans, cattle and pigs. First, *Sorex*, *Felis*, *Mustela*, *Phoca*, *Tursiops*, *Equus*, *Eulemur*, *Ateles*, *Callithrix*, *Cebus*, *Macaca*, *Colobus* and *Presbytis* all possess a chromosome that is jointly painted by h14 and h15. In the three species of Old World monkey (*Macaca*, *Presbytis* and *Colobus*), h14 and h15 paint no other chromosome. In contrast, h14 and h15 paint different chromosomes in *H. concolor*, *H. lar*, *H. syndactylus*, *Pongo*, *Gorilla* and *Pan*. These observations suggest that h(14 + 15) was an ancestral linkage group in the werepig and in our common ancestor with Old World monkeys but that this chromosome underwent fission in the lineage leading to apes. Second, the mapping of {*NP*} to h14/c10/p7, {*IGH@*} to h14/c21/p7, {*PKM2*} to h15/c10/p7 and {*MPI*} to h15/c21/p7 suggests that the separation of loci to c10 and c21 occurred after the common ancestor of pigs and cattle. Third, there seems to have been a reciprocal translocation in the pig lineage between the homologue of h6 and the homologue of h(14 + 15) because p1 and p7 are both painted by h6, as well as by h14 and h15.

Loci from h14 and h15 are therefore proposed to have been located on a single chromosome in the werepig. This chromosome is then hypothesized to have undergone independent centric fissions in human and cattle ancestry, and to have undergone a reciprocal translocation during pig ancestry. There seems to have been a pericentric inversion in the artiodactyl lineage because loci from both h14 and h15 are found on c10, c21 and p7. This inversion occurred in the artiodactyl lineage, rather than the primate lineage, because genes on h14 map to m12 and m14, whereas genes on h15 map to m2, m7 and m9. If the inversion had occurred in the primate lineage, one would expect loci from h14 and h15 to map to overlapping sets of mouse chromosomes. Nevertheless, the observation that loci from h14 and h15 map to non-overlapping sets of chromosomes in mice (and rats) is curious because, although there is strong evidence that h14 and h15 were linked in the werepig, there is little evidence of a shared earlier history. (These arguments are predicated on the hypothesis that primates and artiodactyls are more closely related to each other than either is to mice.)

As noted previously (§ 4(l)), loci from h11 and h15 map close together on m2, m7 and m9 (Elliott 1996). This juxtaposition of loci is compatible with the existence of an ancestral h15/m(2 + 7 + 9) linkage group in the weremouse. An ancient association of h15/m2 and h15/m7 is supported by the mapping of {*B2M*} from h15/m2 and {*IGF1R*, *AGC1*} from h15/m7 to the same microchromosome of chickens (Jones *et al*. 1997). The early history of the h14/m12 and h14/m14 cells is unclear.

(p) *Human chromosome 16*

Human chromosome 16 paints a single chromosome in *Macaca*, *Colobus*, *Pongo*, *Gorilla* and *Pan*, but two chromosomes in *Presbytis*, *Ateles*, *Callithrix*, *Cebus*, *Eulemur*, *Sorex*, *Tursiops*, *Equus*, *Felis*, *Phoca*, *Mustela*, *Bos* (c18, c29) and *Sus* (p3, p6). Therefore an equivalent of h16 was probably present in the common ancestor of Old World monkeys and apes, but might have been absent from the common ancestor of catarrhine and platyrrhine primates. In *Eulemur*, the two chromosomes painted by h16 are not painted by any other human chromosome. In four species of platyrrhine primates (*Ateles*, *Callithrix*, *Cebus*, *Alouatta*), h10 and h16 paint a shared chromosome. However, this combination is absent from all other species in table 1 (except *Phoca*, in which the combination is probably derived independently).

Synteny of loci from the two arms of h16 seems to be limited to catarrhine primates. Therefore the ancestries of h16p and h16q will be considered separately. Loci from human 16q map to a single chromosome in cattle (c18), pigs (p6), rats (r19) and mice (m8). Thus, 'h16q' seems to have been conserved as an ancestral linkage block in all these species since they diverged from the weremouse.

The karyotypes of *Mustela*, *Phoca*, *Felis*, *Tursiops*, *Muntiacus*, *Bos* and *Sus* all contain a chromosome that is painted by both h16 and h19. Reciprocal painting in *Felis* and *Sus* (and comparative mapping in cattle and humans) suggest that this chromosome combines loci of human 16q and 19q (Goureau *et al*. 1996; Wienberg *et al*. 1997). Chromosome painting also detects an h(16q + 19q) linkage block in *Sorex*: h16 paints segments of two chromosome arms, one of which (arm h) is painted by h19 (h16 and h19 paint adjacent segments); furthermore, {*GOT2*} from h16q and {*PEPD*} from h19q have both been mapped to arm h (Dixkens *et al*. 1998). The interpretation of these observations depends on the phylogenetic placement of *Sorex*. If *Sorex* is an outgroup to primates and ferungulates, the sharing of h(16q + 19q) synteny by shrews, artiodactyls and carnivores suggests that loci of h16q and h19q were syntenic in the werepig (and in the earlier common ancestor of humans and shrews). If, however, primates are an outgroup to shrews plus ferungulates, h(16q + 19q) could be either a synapomorphy that unites shrews, artiodactyls and carnivores, or a symplesiomorphy that has been lost in primates. Although the evidence is subject to alternative interpretations, § 3c and table 4 propose that h(16q + 19q) was an ancestral linkage group of the werepig.

Among primates, h16 and h19 paint a shared chromosome in *Eulemur macaco macaco* (Müller *et al*. 1997). However, reciprocal painting reveals that this chromosome combines loci from h16q and h19p (rather than h19q). Moreover, the association is absent from *E. fulvus mayottensis*. Evidence of an h(16q + 19q) association is lacking in rodents: loci of h16q map to m8/r19, whereas loci of h19q map to m7/r1.

Loci from human 16p map to at least four mouse chromosomes (m7, m11, m16, m17). The h16p/m11, h16p/m16 and h16p/m17 cells were almost certainly linked to each other in the common ancestor of rats and mice (and in the weremouse) because loci from all three cells map to r10: {*MPG*} from m11, {*GSPT1*, *PRM1*, *GRIN2A*} from m16, and {*TSC2*, *PKD1*} from m17. The ancestral linkage of h16p/m(11 + 17) is also indicated by the presence of *Hba* on m11 and *Hba-ps4* (an unprocessed α-globin pseudogene) on m17 (Tan & Whitney 1993).

Whether h16p/m7 was linked to h16p/m(11 + 16 + 17) in the weremouse is unclear. However, these blocks were clearly linked in the werepig because both contain genes that map to c25 and p3. Therefore a linkage block corresponding to h16p seems to have been present in the werepig, but whether this block was associated with loci from any other human chromosome is uncertain. The karyotypes of *Mustela*, *Tursiops*, *Bos* and *Sus* contain a chromosome with homology to both h7 and h16 (comparative mapping suggests that this chromosome shares loci with h16p) but I have found no evidence to suggest that an h(7 + 16p) linkage group was present in the werepig.

Distal 16p has been evolutionarily unstable in the recent past. *Il9r* maps close to *Hba* on m11 and an *IL9R* pseudogene is located near *HBA* on human 16p13.3. However, the functional *IL9R* gene of humans is located in the Xq/Yq pseudoautosomal region. A copy of *IL9R* is present on Xq of chimpanzees and gorillas, but the Y-linked gene is unique to humans. Thus, there seems to have been a recent translocation of autosomal material from distal '16p' to the X chromosome and an even more recent translocation from the X to the Y chromosome (Kermouni *et al*. 1995; Vermeesch *et al*. 1997). Sequences related to the *IL9R* pseudogene have also been translocated to the telomeric regions of chromosomes 9q, 10p and 18p (Flint *et al*. 1997). Telomeric 16p has three common alleles: the A and C alleles differ in length by 260 kb; the B allele is intermediate in size but contains sequences that are unrelated to the A and C alleles (Wilkie *et al*. 1990; Wilkie & Higgs 1992). The telomeres of Xq and Yq are almost identical in sequence to allele A (Flint *et al*. 1997). A further example of recent instability is the duplication of sequences related to *PKD1* from 16p13.3 to 16p13.1 (European Polycystic Kidney Disease Consortium 1994).

Trisomy 16 is the most common human trisomy. It is estimated to occur in about 1.5% of late first trimester pregnancies, with most cases lost at around 12 weeks of gestation (Wolstenholme 1995). Diagnosed cases are overwhelmingly of maternal meiotic origin and show a striking reduction of recombination in the pericentromeric region (Hassold *et al*. 1995). Non-disjunction of h16 might have different causes from non-disjunction of other human chromosomes because the risk of trisomy does not show the marked increase with advanced maternal age that is observed for the other smaller chromosomes (Risch *et al*. 1986). Strong segregation distortion of a familial translocation t(10;16)(q26.3; p13.1) has been reported in one pedigree, but in this case it was the derivative chromosome with the h10 centromere that was transmitted to all 21 out of 21 offspring (Resta *et al*. 1996).

The chromosome's high rate of non-disjunction in female meiosis might be related to unusual features of its pericentromeric region. The large block of constitutive heterochromatin at proximal 16q is polymorphic in size (Verma *et al*. 1978), and proximal 16p has been the integration site for duplicated material from at least four

other chromosomes (Eichler 1998): immunoglobulin V_H segments from h14 are duplicated at 16p11.2 (Tomlinson *et al.* 1994); sequences are shared by 15q11–q13 and 16p11.2 (Buiting *et al.* 1992); a 26.5 kb segment from Xq28 is duplicated at 16p11.1 (Eichler *et al.* 1996); and 16p11 is polymorphic for material duplicated from 6p25 (Z. Wong *et al.* 1990). Moreover, chromosome 16-specific repetitive sequences are duplicated on either side of the h16 centromere (Dauwerse *et al.* 1992; Stallings *et al.* 1992). A variant chromosome with an extra euchromatic band in 16p has been described from asymptomatic carriers in several independent families (Thompson & Roberts 1987; Bogart *et al.* 1991).

(q) *Human chromosome 17*

Human chromosome 17 is conserved largely (or completely) intact on c19, s11, p12, r10 and m11 (Eppig & Nadeau 1995; Yang & Womack 1995). At the time of writing, h17/m11 contained more mapped loci than any other cell of the Oxford Grid. h17 paints a single chromosome that is painted by no other human chromosome in *Pan*, *Pongo*, *Macaca*, *Presbytis*, *Ateles*, *Cebus*, *Eulemur*, *Sorex*, *Felis*, *Equus*, *Tursiops*, *Bos* and *Sus*. Despite this remarkable conservation, there is no absolute barrier to disruption of h17: gorillas possess a reciprocal translocation between the homologues of h5 and h17 (Stanyon *et al.* 1992); and h17 paints two (or more) chromosomes in *Hylobates lar* (Jauch *et al.* 1992), *Colobus guereza* (Bigoni *et al.* 1997*b*), *Alouatta seniculus arctoidea* (Consigliere *et al.* 1996) and *Canis familiaris* (Werner *et al.* 1997). Sequences related to *NF1* at 17q11.2 have recently been dispersed to several pericentric locations in the human genome (Régnier *et al.* 1997).

(r) *Human chromosome 18*

Human chromosome 18 paints a single chromosome in *Pan*, *Gorilla*, *Pongo*, *Hylobates*, *Macaca*, *Presbytis*, *Colobus*, *Ateles*, *Alouatta*, *Cebus*, *Callithrix*, *Eulemur*, *Sorex*, *Felis*, *Mustela*, *Phoca*, *Equus*, *Tursiops* and *Bos* (c24). Moreover, most loci that have been jointly mapped in humans and mice belong to h18/m18. These data suggest that the bulk of h18 has been conserved intact in all these species since their last common ancestor. In contrast, h18 paints two chromosomes in *Sus* (p1, p6). When pig chromosomes were used to paint human chromosomes, p1 painted all of h18 except 18q11–q12, which was painted by p6 (Goureau *et al.* 1996). {*MC2R*, *FECH*, *MBP*} map to h18/c24/m18 (outside 18q11–q12), whereas {*TTR*} maps to h18/p6/c24/m18. Therefore the separation of h18/p6 and h18/p1 seems to have occurred in the pig lineage, at some time after the most recent common ancestor of cattle and pigs.

The chromosome painted by h18 is not painted by any other human chromosome in *Pan*, *Gorilla*, *Pongo*, *Macaca*, *Presbytis*, *Colobus* and *Bos*, but h8 and h18 paint a shared chromosome in *Cebus*, *Callithrix*, *Ateles* and *Alouatta*. In *Felis*, *Mustela*, *Equus* and *Tursiops*, the chromosome painted by h18 is also painted by h12 and h22.

(s) *Human chromosome 19*

Human chromosome 19 paints a single chromosome in *Pan*, *Gorilla*, *Pongo*, *Macaca*, *Ateles*, *Alouatta*, *Cebus* and *Callithrix*, but paints two chromosomes in *Colobus*, *Presbytis*, *Eulemur*, *Bos* (c7, c18), *Sus* (p2, p6), *Tursiops*, *Felis*, *Phoca*, *Mustela* and *Equus*. Loci on 19p map to c7/p2/m(7 + 17), whereas loci on 19q map to c18/p6/m(8 + 9 + 10 + 17). Therefore a chromosomal equivalent of h19 seems to have been present in the common ancestor of Old World and New World monkeys, but loci from h19p and h19q are unlinked in most other species for which there are data. h19 paints a single segment of a single chromosome of *S. araneus*, to which chromosome {*PEPD*} from h19q has also been mapped (Dixkens *et al.* 1998). This could be interpreted as evidence for an earlier association of the two arms of h19 but such a conclusion seems premature because the possibility remains that a distinct region of homology to 19p was not recognized by the h19 'paint'. So far, no loci from h19p have been mapped in *Sorex*.

Human 19q is preserved largely intact on m7, except for a 2 Mb segment at 19q13.4 that is homologous to m17 (Stubbs *et al.* 1996). None of the genes from this 2 Mb segment have been mapped in artiodactyls and I am unable to infer its history. Loci of 19q are linked to loci of 16q in *Bos*, *Sus*, *Tursiops*, *Felis*, *Phoca*, *Mustela* and *Sorex*. The evidence that h(19q + 16q) is an ancestral association of the werepig and weremouse is reviewed in § 4(p).

Loci of 19p are linked to loci from h5 in *Bos*, *Sus* and *Tursiops*—and to loci from h3 in *Felis*, *Phoca* and *Mustela*—but neither of these associations is found in primates, rats or mice. The h19p/p2 grid-cell contains loci that map to m8 {*INSL3*, *INSR*, *NFIX*}, m9 {*ACP5*}, m10 {*AMH*} and m17 {*C3*}. Therefore h19p/c7/p2/m(8 + 9 + 10 + 17) can be inferred to have been an ancestral linkage block of the werepig, but I have found few clues about its earlier history. The occurrence of loci from m17 on both 19p and 19q seems to be coincidental rather than evidence of conserved ancestral linkage.

h19 (like h16) is polymorphic for a pericentromeric insertion of DNA from another chromosome. Part of the integrin β1 gene (*ITGB1*) from pericentromeric h10 is duplicated at proximal 19p (*FNRBL*). This insertion occurs at frequencies of 20–80% in all human populations sampled (Giuffra *et al.* 1990; Kidd *et al.* 1991). The *FNRBL* sequence was considered unlikely to be functional because it was not present in all individuals (Giuffra *et al.* 1990). However, the insertion's high frequency in diverse human populations suggests that it is maintained as a selectively balanced polymorphism. Mendelian variation in centromeric staining has been reported for h19 (Crossen 1975; Gardner & Wood 1979), but has not been related to the presence or absence of *FNRBL*.

There are no well-documented cases of trisomy 19 among human aborted foetuses or live births (Hassold & Jacobs 1984). Presumably, such trisomies occur but are lost very early in development. Chromosome 19q carries several loci that might have important roles in maternal–embryonic relationships. These include the human chorionic gonadotropin gene cluster (*CGB@*), the pregnancy-specific b_1-glycoprotein gene cluster (*PSG@*), the natural killer cell inhibitory receptors (*KIR@*) and the placental IgG receptor (*FCGRT*). Two recent studies have reported segregation distortion for loci on 19q, one in paternal transmissions (Carey *et al.* 1994) and the other in maternal transmissions (Evans *et al.* 1994).

(t) *Human chromosome 20*

Human chromosome 20 paints two chromosomes in *H. concolor* (Koehler *et al.* 1995*b*) but paints a single chromosome in all other species listed in table 1. At the time

of writing, all loci from h20 that have been mapped in mice are located on distal m2. The h20/m2 cell might have been linked to h2b/m2 in the werepig (§ 4b).

(u) *Marker chromosomes*

An extra 'marker' chromosome is detected in about one in 1000 prenatal diagnoses (Hook & Cross 1987; Sachs *et al*. 1987; Blennow *et al*. 1994; Brøndrum-Nielsen & Mikkelsen 1995), and a similar frequency is found among newborn infants (Gravholt & Friedrich 1995). Approximately half of these supernumerary chromosomes have originated *de novo* (i.e. are absent from parental karyotypes) and half are inherited (i.e. are present in a parental karyotype). Marker chromosomes derived from the short arm and pericentric region of chromosome 15 are particularly common (Blennow *et al*. 1994; Webb 1994). Most children with marker chromosomes have a normal phenotype (Gravholt & Friedrich 1995). These data are mentioned here, not because any of the marker chromosomes reach frequencies that would justify their classification as fully-fledged B chromosomes, but because the extensive literature on human 'markers' provides a wealth of information for evolutionary biologists interested in the origin of B chromosomes in other species.

This paper could not have been written without the staffs of the Countway Medical Library and the various genome databases. I especially thank Dave Shaw at the Mouse Genome Database for prompt replies on homology queries. Lucas Mix and Yvonne Parsons made helpful comments on the manuscript.

REFERENCES

Amadou, C., Ribouchon, M. T., Mattei, M. G., Jenkins, N. A., Gilbert, D. J., Copeland, N. G., Avoustin, P. & Pontarotti, P. 1995 Localization of new genes and markers to the distal part of the human major histocompatibility complex (MHC) region and comparison with the mouse: new insights into the evolution of mammalian genomes. *Genomics* **26**, 9–20.

Bielec, P. E., Gallagher, D. S., Womack, J. E. & Busbee, D. L. 1998 Homologies between human and dolphin chromosomes detected by heterologous chromosome painting. *Cytogenet. Cell Genet*. **81**, 18–25.

Bigoni, F., Koehler, U., Stanyon, R., Ishida, T. & Wienberg, J. 1997*a* Fluorescence in situ hybridization between human and silvered leaf monkey chromosomes, reveals reciprocal translocations between chromosomes homologous to human Y/5, 1/9, and 6/16, and delineates an $X_1X_2Y_1Y_2/X_1X_1X_2X_2$ sex-chromosome system. *Am. J. Phys. Anthropol*. **23**, 315–327.

Bigoni, F., Stanyon, R., Koehler, U., Morescalchi, A. M. & Wienberg, J. 1997*b* Mapping homology between human and black and white colobine monkey chromosomes by fluorescent in situ hybridization. *Am. J. Primatol*. **42**, 289–298.

Blake, J. A., Eppig, J. T., Richardson, J. E., Davisson, M. T. & the Mouse Genome Informatics Group 1998 The Mouse Genome Database (MGD): a community resource. Status and enhancements. *Nucleic Acids Res*. **26**, 130–137.

Blennow, E., Bui, T.-H., Kristoffersson, U., Vujic, M., Annerén, G., Holmberg, E. & Nordenskjöld, M. 1994 Swedish survey of extra structurally abnormal chromosomes in 39 105 consecutive prenatal diagnoses: prevalence and characterization by fluorescence *in situ* hybridization. *Prenatal Diagn*. **14**, 1019–1028.

Bogart, M. H., Bradshaw, C. & Jones, O. W. 1991 Prenatal diagnosis of euchromatic 16p+ heteromorphisms in two unrelated families. *Prenatal Diagn*. **11**, 417–418.

Borowik, O. A. 1995 Coding chromosomal data for phylogenetic analysis: phylogenetic resolution of the *Pan–Homo–Gorilla* trichotomy. *Syst. Biol*. **44**, 563–570.

Brøndrum-Nielsen, K. & Mikkelsen, M. 1995 A 10-year survey, 1980–1990, of prenatally diagnosed small supernumerary marker chromosomes, identified by FISH analysis. Outcome and follow-up of 14 cases diagnosed in a series of 12 699 prenatal samples. *Prenatal Diagn*. **15**, 615–619.

Bruch, J., Rettenberger, G., Leeb, T., Meier-Ewert, S., Klett, C., Brenig, B. & Hameister, H. 1996 Mapping of type I loci from human chromosome 7 reveals segments of conserved synteny on pig chromosomes 3, 9, and 18. *Cytogenet. Cell Genet*. **73**, 164–167.

Buckton, K. E., O'Riordan, M. L., Ratcliffe, S., Slight, J., Mitchell, M., McBeath, S., Keay, A. J., Barr, D. & Short, M. 1980 A G-band study of chromosomes in live infants. *Ann. Hum. Genet*. **43**, 227–239.

Buiting, K., Greger, B., Brownstein, B. H., Mohr, R. M., Voiculescu, I., Winterpacht, A., Zabel, B. & Horsthemke, B. 1992 A putative gene family in 15q11–13 and 16p11.2: possible implications for Prader–Willi and Angelman syndromes. *Proc. Natl Acad. Sci. USA* **89**, 5457–5461.

Burt, D. W., Bumstead, N., Bitgood, J. J., Ponce de Leon, F. A. & Crittenden, L. B. 1995 Chicken genome mapping: a new era in avian genetics. *Trends Genet*. **11**, 190–194.

Cacurri, S., Piazzo, N., Deidda, G., Vigneti, E., Galluzzi, G., Colantoni, L., Merico, B., Ricci, E. & Felicetti, L. 1998 Sequence homology between 4qter and 10qter loci facilitates the instability of subtelomeric *Kpn*I repeat units implicated in facioscapulohumeral muscular dystrophy. *Am. J. Hum. Genet*. **63**, 181–190.

Cao, Y., Janke, A., Waddell, P. J., Westerman, M., Takenaka, O., Murata, S., Okada, N., Pääbo, S. & Hasegawa, M. 1998 Conflict among individual mitochondrial proteins in resolving the phylogeny of eutherian orders. *J. Mol. Evol*. **47**, 307–322.

Carey, N. (and 11 others) 1994 Meiotic drive at the myotonic dystrophy locus? *Nature Genet*. **6**, 117–118.

Carver, E. A. & Stubbs, L. 1997 Zooming in on the human–mouse comparative map: genome conservation re-examined on a high-resolution scale. *Genome Res*. **7**, 1123–1137.

Chan, P., Simon-Chazottes, D., Mattei, M. G., Guenet, J. L. & Salier, J. P. 1994 Comparative mapping of lipocalin genes in human and mouse: the four genes for complement C8 γ chain, prostaglandin-D-synthase, oncogene-24P3, and progestagen-associated endometrial protein map to HSA9 and MMU2. *Genomics* **23**, 145–150.

Chowdhary, B. P., Frönicke, L., Gustavsson, I. & Scherthan, H. 1996 Comparative analysis of the cattle and human genomes: detection of ZOO-FISH and gene mapping-based chromosomal homologies. *Mammal. Genome* **7**, 297–302.

Christensen, K., Lomholt, B., Hallenberg, C. & Nielsen, K. V. 1998 Mink 5S rRNA genes map to 2q in three loci suggesting conservation of synteny with human 1q. *Hereditas* **128**, 17–20.

Collinson, M. N., Fisher, A. M., Walker, J., Currie, J., Williams, L. & Roberts, P. 1997 Inv(10)(p11.2q21.2), a variant chromosome. *Hum. Genet*. **101**, 175–180.

Comparative Genome Organization; First International Workshop 1996 Comparative genome organization in vertebrates. *Mammal. Genome* **7**, 717–734.

Consigliere, S., Stanyon, R., Koehler, U., Agoramoorthy, G. & Wienberg, J. 1996 Chromosome painting defines genomic rearrangements between red howler monkey subspecies. *Chromosome Res*. **4**, 264–270.

Crossen, P. E. 1975 Variation in the centromeric banding of chromosome 19. *Clin. Genet*. **8**, 218–222.

Daniel, A., Hook, E. B. & Wulf, G. 1988 Collaborative USA data on prenatal diagnosis for parental carriers of chromosome rearrangements: risks for unbalanced progeny. In *The*

cytogenetics of mammalian autosomal rearrangements (ed. A. Daniel), pp. 73–162. New York: Alan R. Liss.

Dauwerse, J. G., Jumelet, E. A., Wessels, J. W., Saris, J. J., Hagemeijer, A., Beverstock, G. C., Van Ommen, G. J. B. & Breuning, M. H. 1992 Extensive cross-homology between the long and the short arm of chromosome 16 may explain leukemic inversions and translocations. *Blood* **79**, 1299–1304.

Delarbre, C., Nakauchi, H., Bontrop, R., Kourilsky, P. & Gachelin, G. 1993 Duplication of the CD8 β-chain gene as a marker of the man–gorilla–chimpanzee clade. *Proc. Natl Acad. Sci. USA* **90**, 7049–7053.

Dixkens, C., Klett, C., Bruch, J., Kollak, A., Serov, O. L., Zhdanov, N., Vogel, W. & Hameister, H. 1998 ZOO-FISH analysis in insectivores: 'evolution extols the virtue of the status quo.' *Cytogenet. Cell Genet.* **80**, 61–67.

Eichler, E. E. 1998 Masquerading repeats: paralogous pitfalls of the human genome. *Genome Res.* **8**, 758–762.

Eichler, E. E., Lu, F., Shen, Y., Antonacci, R., Jurecic, V., Doggett, N. A., Moyzis, R. K., Baldini, A., Gibbs, R. A. & Nelson, D. L. 1996 Duplication of a gene-rich cluster between 16p11.1 and Xq28: a novel pericentromeric-directed mechanism for paralogous genome evolution. *Hum. Mol. Genet.* **5**, 899–912.

Eichler, E. E., Budarf, M. L., Rocchi, M., Deaven, L. L., Doggett, N. A., Baldini, A., Nelson, D. L. & Mohrenweiser, H. W. 1997 Interchromosomal duplications of the adrenoleukodystrophy locus: a phenomenon of pericentromeric plasticity. *Hum. Mol. Genet.* **6**, 991–1002.

Elliott, R. 1996 Comparative maps of human chromosome 11 and the mouse. *Cytogenet. Cell Genet.* **74**, 37–42.

Eppig, J. T. & Nadeau, J. H. 1995 Comparative maps: the mammalian jigsaw puzzle. *Curr. Opin. Genet. Dev.* **5**, 709–716.

Ermert, K., Mitlöhner, H., Schempp, W. & Zachau, H. G. 1995 The immunoglobulin κ locus of primates. *Genomics* **25**, 623–629.

European Polycystic Kidney Disease Consortium 1994 The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region in chromosome 16. *Cell* **77**, 881–894.

Evans, K., Fryer, A., Inglehearn, C., Duvall-Young, J., Whittaker, J. L., Gregory, C. Y., Butler, R., Ebenezer, N., Hunt, D. M. & Bhattacharya, S. 1994 Genetic linkage of cone–rod retinal dystrophy to chromosome 19q and evidence for segregation distortion. *Nature Genet.* **6**, 210–213.

Flint, J., Thomas, K., Micklem, G., Raynham, H., Clark, K., Doggett, N. A., King, A. & Higgs, D. R. 1997 The relationship between chromosome structure and function at a human telomeric region. *Nature Genet.* **15**, 252–257.

Fontdevila, A. 1992 Genetic instability and rapid speciation: are they coupled? *Genetica* **86**, 247–258.

Footz, T. K., Birren, B., Minoshima, S., Asakawa, S., Shimizu, N., Riazi, M. A. & McDermid, H. E. 1998 The gene for death agonist BID maps to the region of human 22q11.2 duplicated in cat eye syndrome chromosomes and to mouse chromosome 6. *Genomics* **51**, 472–475.

Fridolfsson, A.-K., Cheng, H., Copeland, N. G., Jenkins, N. A., Liu, H.-C., Raudsepp, T., Woodage, T., Chowdhary, B., Halverson, J. & Ellegren, H. 1998 Evolution of avian sex chromosomes from an ancestral pair of autosomes. *Proc. Natl Acad. Sci. USA* **95**, 8147–8152.

Frippiat, J.-P., Dard, P., Marsh, S., Winter, G. & Lefranc, M.-P. 1997 Immunoglobulin lambda light chain orphons on human chromosome 8q11.2. *Eur. J. Immunol.* **27**, 1260–1265.

Frönicke, L. & Scherthan, H. 1997 Zoo-fluorescence in situ hybridization analysis of human and Indian muntjac karyotypes (*Muntiacus muntjak vaginalis*) reveals satellite DNA clusters at the margins of conserved syntenic segments. *Chromosome Res.* **5**, 254–261.

Frönicke, L., Chowdhary, B. P., Scherthan, H. & Gustavsson, I. 1996 A comparative map of the porcine and human genomes demonstrates ZOO-FISH and gene mapping-based chromosomal homologies. *Mammal. Genome* **7**, 285–290.

Frönicke, L., Müller-Navia, J., Romanakis, K. & Scherthan, H. 1997 Chromosomal homeologies between human, harbor seal (*Phoca vitulina*) and the putative ancestral carnivore karyotype revealed by Zoo-FISH. *Chromosoma* **106**, 108–113.

Gardner, H. A. & Wood, E. M. 1979 Variation in chromosome 19. *J. Med. Genet.* **16**, 79–80.

Gatesy, J. 1997 More DNA support for a Cetacea/Hippopotamidae clade: the blood clotting protein gene γ-fibrinogen. *Mol. Biol. Evol.* **14**, 537–543.

Gelman-Kohan, Z., Rosensaft, J., Nisani Ben-Cohen, R. & Chemke, J. 1993 Homozygosity for inversion (2)(p12q14). *Hum. Genet.* **92**, 427.

Gerecke, D. R., Olson, P. F., Koch, M., Knoll, J. H. M., Taylor, D. L., Champliaud, M.-F., Olsen, B. R. & Burgeson, R. E. 1997 Complete primary structure of two splice variants of collagen XII and assignment of α1(XII) collagen (COL12A1), α1(IX) collagen (COL9A1), and α1(XIX) collagen (COL19A1) to human chromosome 6q12–q13. *Genomics* **41**, 236–242.

Giuffra, L. A. (and 10 others) 1990 Genetic and physical mapping and population studies of a fibronectin receptor β-subunit-like sequence on human chromosome 19. *Genomics* **8**, 340–346.

Gläser, B., Grützner, F., Taylor, K., Schiebel, K., Meroni, G., Tsioupra, K., Toder, R. & Graves, J. A. M. 1998 *CSF2RA*, *ANT3*, and *STS* are autosomal in marsupials: implications for the origin of the pseudoautosomal region of mammalian sex chromosomes. *Mammal. Genome* **9**, 373–376.

Gosden, J. R., Mitchell, A. R., Seuanez, H. N. & Gosden, C. M. 1977 The distribution of sequences complementary to human satellite DNAs I, II and IV in the chromosomes of chimpanzee (*Pan troglodytes*), gorilla (*Gorilla gorilla*) and orang-utan (*Pongo pygmaeus*). *Chromosoma* **63**, 253–271.

Goureau, A., Yerle, M., Schmitz, A., Riquet, J., Milan, D., Pinton, P., Frelat, G. & Gellin, J. 1996 Human and porcine correspondence of chromosome segments using bidirectional chromosome painting. *Genomics* **36**, 252–262.

Gravholt, C. H. & Friedrich, U. 1995 Molecular cytogenetic study of supernumerary marker chromosomes in an unselected group of children. *Am. J. Med. Genet.* **56**, 106–111.

Grewal, P. K., Bolland, D. J., Todd, L. C. & Hewitt, J. E. 1998 High resolution mapping of mouse chromosome 8 identifies an evolutionary chromosomal breakpoint. *Mammal. Genome* **9**, 603–607.

Groupe de Cytogénéticiens Français 1994 Pericentric inversions in man. A French collaborative study. *Annales de Génétique* **29**, 129–168.

Guo, N., Mogues, T., Weremowicz, S., Morton, C. C. & Sastry, K. N. 1998 The human ortholog of mannose-binding protein-A gene is an expressed pseudogene that localizes to chromosome 10. *Mammal. Genome* **9**, 246–249.

Haig, D. 1996*a* Altercation of generations: genetic conflicts of pregnancy. *Am. J. Reprod. Immunol.* **35**, 226–232.

Haig, D. 1996*b* Do imprinted genes have few and small introns? *BioEssays* **18**, 351–353.

Hameister, H., Klett, C., Bruch, J., Dixkens, C., Vogel, W. & Christensen, K. 1997 Zoo-FISH analysis: the American mink (*Mustela vison*) closely resembles the cat karyotype. *Chromosome Res.* **5**, 5–11.

Hassold, T. J. & Jacobs, P. A. 1984 Trisomy in man. *A. Rev. Genet.* **18**, 69–97.

Hassold, T., Merrill, M., Adkins, K., Freeman, S. & Sherman, S. 1995 Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. *Am. J. Hum. Genet.* **57**, 867–874.

Hayes, H. 1995 Chromosome painting with human chromosome-specific DNA libraries reveals the extent and distribution of conserved segments in bovine chromosomes. *Cytogenet. Cell Genet.* **71**, 168–174.

Hedrick, P. W. 1981 The establishment of chromosomal variants. *Evolution* **35**, 322–332.

Hildebrandt, F., Cybulla, M., Strahm, B., Nothwang, H. G., Singh-Sawhney, I., Berz, K., Nicklin, M., Reiner, O. & Brandis, M. 1996 Physical mapping of the gene for juvenile nephronophthisis (NPH1) by construction of a complete YAC contig of 7 Mb on chromosome 2q13. *Cytogenet. Cell Genet.* **73**, 235–239.

Hook, E. B. & Cross, P. K. 1987 Extra structurally abnormal chromosomes (ESAC) detected at amiocentesis: frequency in approximately 75 000 prenatal cytogenetic diagnoses and associations with maternal and paternal age. *Am. J. Hum. Genet.* **40**, 83–101.

Hsu, L. Y. F., Benn, P. A., Tannenbaum, H. L., Perlis, T. E. & Carlson, A. D. 1987 Chromosomal polymorphisms of 1, 9, 16, and Y in 4 major ethnic groups: a large prenatal study. *Am. J. Med. Genet.* **26**, 95–101.

Jackson, M. S., See, C. G., Mulligan, L. M. & Lauffart, B. F. 1996 A 9.75-Mb map across the centromere of human chromosome 10. *Genomics* **33**, 258–270.

Jalal, S. M., Kukolich, M. K., Garcia, M. & Day, D. W. 1990 Euchromatic 9q+ heteromorphism in a family. *Am. J. Med. Genet.* **37**, 155–156.

Jauch, A., Wienberg, J., Stanyon, R., Arnold, N., Tofanelli, S., Ishida, T. & Cremer, T. 1992 Reconstruction of genomic rearrangements in great apes and gibbons by chromosome painting. *Proc. Natl Acad. Sci. USA* **89**, 8611–8615.

Johansson, Å., Helou, K. & Levan, G. 1998 Cytogenetic localization of cancer-related genes in the rat and comparative mapping studies in human and mouse. *Cytogenet. Cell Genet.* **81**, 217–221.

Johansson, M., Ellegren, H. & Andersson, L. 1995 Comparative mapping reveals extensive linkage conservation—but with gene order rearrangements—between the pig and human genomes. *Genomics* **25**, 682–690.

Jones, C. T., Morrice, D. R., Paton, I. R. & Burt, D. W. 1997 Gene homologs on human chromosome 15q21–q26 and a chicken microchromosome identify a new conserved segment. *Mammal. Genome* **8**, 436–440.

Kermouni, A. (and 11 others) 1995 The IL-9 receptor gene (IL9R): genomic structure, chromosomal localization in the pseudoautosomal region of the long arm of the sex chromosomes, and identification of IL9R pseudogenes at 9qter, 10pter, 16pter, and 18pter. *Genomics* **29**, 371–382.

Khaledduzzaman, M., Sumiyoshi, H., Ueki, Y., Inoguchi, K., Ninomiya, Y. & Yoshioka, H. 1997 Structure of the human type XIX collagen (*COL19A1*) gene, which suggests it has arisen from an ancestor gene of the FACIT family. *Genomics* **45**, 304–312.

Kidd, J. R., Black, F. L., Weiss, K. M., Balazs, I. & Kidd, K. K. 1991 Studies of three Amerindian populations using nuclear DNA polymorphisms. *Hum. Biol.* **63**, 775–794.

King, M. 1993 *Species evolution: the role of chromosomal change*. Cambridge University Press.

Kingsmore, S. F., Souryal, C. A., Watson, M. L., Patel, D. D. & Seldin, M. F. 1995 Physical and genetic linkage of the genes encoding Ly-9 and CD48 on mouse and human chromosomes 1. *Immunogenetics* **42**, 59–62.

Klein, S., Morrice, D. R., Sang, H., Crittenden, L. B. & Burt, D. W. 1996 Genetic and physical mapping of the chicken IGF1 gene to chromosome 1 and conservation of synteny with other vertebrate genomes. *J. Hered.* **87**, 10–14.

Koehler, U., Arnold, N., Wienberg, J., Tofanelli, S. & Stanyon, R. 1995*a* Genomic reorganization and disrupted chromosomal synteny in the siamang (*Hylobates syndactylus*) revealed by fluorescence in situ hybridization. *Am. J. Phys. Anthropol.* **97**, 37–47.

Koehler, U., Bigoni, F., Wienberg, J. & Stanyon, R. 1995*b* Genomic reorganization in the concolor gibbon (*Hylobates concolor*) revealed by chromosome painting. *Genomics* **30**, 287–292.

Krettek, A., Gullberg, A. & Arnason, U. 1995 Sequence analysis of the complete mitochondrial DNA molecule of the hedgehog, *Erinaceus europaeus*, and the phylogenetic position of the Liptophyla. *J. Mol. Evol.* **41**, 952–957.

Letovsky, S. I., Cottingham, R. W., Porter, C. J. & Li, P. W. D. 1998 GDB: the Human Genome Database. *Nucleic Acids Res.* **26**, 94–99.

Li, W.-H., Gouy, M., Sharp, P M., O'hUigin, C. & Yang, Y.-W. 1990 Molecular phylogeny of Rodentia, Lagomorpha, Primates, Artiodactyla, and Carnivora and molecular clocks. *Proc. Natl Acad. Sci. USA* **87**, 6703–6707.

Liu, W.-S., Harbitz, I., Gustavsson, I. & Chowdhary, B. P. 1998 Mapping of the porcine erythropoietin gene to chromosome 3p16–p15 and ordering of four related subclones by fiber-FISH and DNA-combing. *Hereditas* **128**, 77–81.

Luciani, M. F., Denizot, F., Savary, S., Mattei, M. G. & Chimini, G. 1994 Cloning of two novel ABC transporters mapping on human chromosome 9. *Genomics* **21**, 150–159.

Lundin, L. G. 1993 Evolution of the vertebrate genome as reflected in paralogous chromosomal regions in man and the house mouse. *Genomics* **16**, 1–19.

Maccarone, P., Watson, J. M., Francis, D., Selwood, L., Kola, I. & Graves, J. A. M. 1992 The evolution of human chromosome 21: evidence from *in situ* hybridization in marsupials and a monotreme. *Genomics* **13**, 1119–1124.

Mancuso, D. J., Tuley, E. A., Westfield, L. A., Lester-Mancuso, T. L., Le Beau, M. M., Sorace, J. M. & Sadler, J. E. 1991 Human von Willebrand factor gene and pseudogene: structural analysis and differentiation by polymerase chain reaction. *Biochemistry* **30**, 253–269.

Masabanda, J., Friedl, R., Sazanov, A., Lahti, J. M., Li, H., Kidd, V. J. & Fries, R. 1998 Mapping of five members of the cyclin gene family on chicken chromosomes by FISH. *Chromosome Res.* **6**, 231–233.

Matveeva, N. M., Khlebodarova, T. M., Karasik, G. I., Rubtsov, N. B., Serov, O. L., Broude, N. E., Modyanov, N. N., Monastyrskaya, G. S. & Ovchinnikov, Y. A. 1987 Chromosomal localization of the gene coding for α-subunit of Na^+,K^+-ATPase in the American mink (*Mustela vison*). *FEBS Lett.* **217**, 42–44.

Milatovitch, A., Kitamura, T., Miyajima, A. & Francke, U. 1993 Gene for the α-subunit of the human interleukin-3 receptor (IL3RA) localized to the X–Y pseudoautosomal region. *Am. J. Hum. Genet.* **53**, 1146–1153.

Messer, L. A. (and 10 others) 1997 Mapping of the melatonin receptor 1a (*MTNR1A*) gene in pigs, sheep, and cattle. *Mammal. Genome* **8**, 368–370.

Monfouilloux, S., Avet-Loiseau, H., Amarger, V., Balazs, I., Pourcel, C. & Vergnaud, G. 1998 Recent human-specific spreading of a subtelomeric domain. *Genomics* **51**, 165–176.

Morescalchi, M. A., Schempp, W., Consigliere, S., Bigoni, F., Wienberg, J. & Stanyon, R. 1997 Mapping chromosomal homology between humans and the black-handed spider monkey by fluorescence *in situ* hybridization. *Chromosome Res.* **5**, 527–536.

Müller, S., O'Brien, P. C. M., Ferguson-Smith, M. A. & Wienberg, J. 1997 Reciprocal chromosome painting between human and prosimians (*Eulemur macaco macaco* and *E. fulvus mayottensis*). *Cytogenet. Cell Genet.* **78**, 260–271.

Oh, S. P., Taylor, R. W., Gerecke, D. R., Rochelle, J. M., Seldin, M. F. & Olsen, B. R. 1992 The mouse α1(XII) and human

α1(XII)-like collagen genes are localized on mouse chromosome 9 and human chromosome 6. *Genomics* **14**, 225–231.

Onuma, M., Kusakabe, T. & Kusakabe, S. 1998 Phylogenetic positions of Insectivora in Eutheria inferred from mitochondrial cytochrome *c* oxidase subunit II gene. *Zool. Sci.* **15**, 139–145.

Patton, S. J., Luke, G. N. & Holland, P. W. H. 1998 Complex history of a chromosomal paralogy region: insights from amphioxus aromatic amino acid hydroxylase genes and insulin-related genes. *Mol. Biol. Evol.* **15**, 1373–1380.

Pébusque, M.-J., Coulier, F., Birnbaum, D. & Pontarotti, P. 1998 Ancient large-scale genome duplications: phylogenetic and linkage analyses shed light on chordate genome evolution. *Mol. Biol. Evol.* **15**, 1145–1159.

Penny, D. & Hasegawa, M. 1997 The platypus put in its place. *Nature* **387**, 549–550.

Popescu, C. P., Long, S., Riggs, P., Womack, J., Schmutz, S., Fries, R. & Gallagher, D. S. 1996 Standardization of cattle karyotype nomenclature: report of the committee for the standardization of the cattle karyotype. *Cytogenet. Cell Genet.* **74**, 259–261.

Postlethwait, J. H. (and 28 others) 1998 Vertebrate genome evolution and the zebrafish gene map. *Nature Genet.* **18**, 345–349.

Purvis, A. 1995 A composite estimate of primate phylogeny. *Phil. Trans. R. Soc. Lond.* B **348**, 405–421.

Qiu, Y., Helou, K., Asp, E. & Levan, G. 1997 Regional mapping of the *Mlvi2* locus to rat chromosome 2q16 by FISH. *Hereditas* **127**, 263–264.

Raudsepp, T., Frönicke, L., Scherthan, H., Gustavsson, I. & Chowdhary, B. P. 1996 Zoo-FISH delineates conserved chromosomal segments in horse and man. *Chromosome Res.* **4**, 218–225.

Reddy, K. S. 1996 Variants of chromosome 9 with additional euchromatic bands: two case reports. *Am. J. Med. Genet.* **64**, 536–538.

Régnier, V., Meddeb, M., Lecointre, G., Richard, F., Duverger, A., Nguyen, V. C., Dutrillaux, B., Bernheim, A. & Danglot, G. 1997 Emergence and scattering of multiple neurofibromatosis (*NF1*)-related sequences during hominoid evolution suggest a process of pericentromeric interchromosomal transposition. *Hum. Mol. Genet.* **6**, 9–16.

Resta, R. G., Luthardt, F. & Kapur, R. 1996 Follow-up of a familial translocation t(10;16) with an unusual segregation pattern. *Am. J. Med. Genet.* **63**, 363–365.

Rettenberger, G., Klett, C., Zechner, U., Kunz, J., Vogel, W. & Hameister, H. 1995*a* Visualization of the conservation of synteny between humans and pigs by heterologous chromosome painting. *Genomics* **26**, 372–378.

Rettenberger, G., Klett, C., Zechner, U., Bruch, J., Just, W., Vogel, W. & Hameister, H. 1995*b* ZOO-FISH analysis: cat and human karyotypes closely resemble the putative ancestral mammalian karyotype. *Chromosome Res.* **3**, 479–486.

Richard, F. & Dutrillaux, B. 1998 Origin of human chromosome 21 and its consequences: a 50-million-year-old story. *Chromosome Res.* **6**, 263–268.

Richard, F., Lombard, M. & Dutrillaux, B. 1996 ZOO-FISH suggests a complete homology between human and capuchin monkey (Platyrrhini) euchromatin. *Genomics* **36**, 417–423.

Risch, N., Stein, Z., Kline, J. & Warburton, D. 1986 The relationship between maternal age and chromosome size in autosomal trisomy. *Am. J. Hum. Genet.* **39**, 68–78.

Rousset, D., Agnès, F., Lachaume, P., André, C. & Galibert, F. 1995 Molecular evolution of genes encoding receptor tyrosine kinase with immunoglobulinlike domains. *J. Mol. Evol.* **41**, 421–429.

Sachs, E. S, Van Hemel, J. O., den Hollander, J. C. & Jahoda, M. G. J. 1987 Marker chromosomes in a series of 10 000 prenatal diagnoses. Cytogenetic and follow-up studies. *Prenatal Diagn.* **7**, 81–89.

Scohy, S., Van Vooren, P., Szpirer, C. & Szpirer, J. 1998 Assignment of Sp genes to rat chromosome bands 7q36 (*Sp1*), 10q31→q32.1 (*Sp2*), 3q24→q31 (*Sp3*) and 6q33 (*Sp4*) and of the SP2 gene to human chromosome bands 17q21.3→q22 by in situ hybridization. *Cytogenet. Cell Genet.* **81**, 273–274.

Serov, O. L., Gradov, A. A., Rubtsov, N. B., Zhdanov, N. S., Pack, S. D., Sukoyan, M. A., Mullakandov, M. R. & Zakijn, S. M. 1987 Genetic map of the American mink: gene conservation and organization of chromosomes. In *Isozymes: current topics in biological and medical research. 15. Genetics, development, and evolution* (ed. M. C. Rattazzi, J. G. Scandalios & G. S. Whitt), pp. 179–215. New York: Alan R. Liss.

Sherlock, J. K., Griffin, D. K., Delhanty, J. D. A. & Parrington, J. M. 1996 Homologies between human and marmoset (*Callithrix jacchus*) chromosomes revealed by comparative chromosome painting. *Genomics* **33**, 214–219.

Shimamura, M., Yasue, H., Ohshima, K., Abe, H., Kato, H., Kishiro, T., Goto, M., Munechika, I. & Okada, N. 1997 Molecular evidence from retroposons that whales form a clade within even-toed ungulates. *Nature* **388**, 666–670.

Sinclair, A. H. & Graves, J. A. M. 1991 Gene mapping in marsupials: detection of an ancient autosomal gene cluster. *Genomics* **9**, 581–586.

Solinas-Toldo, S., Lengauer, C. & Fries, R. 1995 Comparative genome map of human and cattle. *Genomics* **27**, 489–496.

Sonstegard, T. S., Kappes, S. M., Keele, J. W. & Smith, T. P. L. 1998 Refinement of bovine chromosome 2 linkage map near the *mh* locus reveals rearrangements between the bovine and human genomes. *Animal Genet.* **29**, 341–347.

Spurdle, A. B., Maccarone, P., Toder, R., Wilcox, S. A. & Graves, J. A. M. 1997 Shared synteny between human chromosome 10 and chromosome 1 of the marsupial tammar wallaby, *Macropus eugenii*. *Cytogenet. Cell Genet.* **77**, 242–245.

Stallings, R. L., Doggett, N. A., Okumura, K. & Ward, D. C. 1992 Chromosome 16-specific repetitive DNA sequences that map to chromosomal regions known to undergo breakage/rearrangement in leukemia cells. *Genomics* **13**, 332–338.

Stanhope, M. J., Smith, M. R., Waddell, V. G., Porter, C. A., Shivji, M. S. & Goodman, M. 1996 Mammalian evolution and the interphotoreceptor retinoid binding protein (IRBP) gene: convincing evidence for several superordinal clades. *J. Mol. Evol.* **43**, 83–92.

Stanhope, M. J., Waddell, V. G., Madsen, O., de Jong, W. W., Cleven, G. C., Kao, D. & Springer, M. S. 1998 Molecular evidence for multiple origins of Insectivora and for a new order of endemic African insectivore mammals. *Proc. Natl Acad. Sci. USA* **95**, 9967–9972.

Stanyon, R., Wienberg, J., Romagno, D., Bigoni, F., Jauch, A. & Cremer, T. 1992 Molecular and classical cytogenetic analyses demonstrate an apomorphic reciprocal chromosomal translocation in *Gorilla gorilla*. *Am. J. Phys. Anthropol.* **88**, 245–250.

Stubbs, L., Carver, E. A., Shannon, M. E., Kim, J., Geisler, J., Generoso, E. E., Stanford, B. G., Dunn, W. C., Mohrenweiser, H., Zimmermann, W., Watt, S. M. & Ashworth, L. K. 1996 Detailed comparative map of human chromosome 19q and related regions of the mouse genome. *Genomics* **35**, 499–508.

Tan, H. & Whitney, J. B. 1993 Genomic rearrangement of the α-globin gene complex during mammalian evolution. *Biochem. Genet.* **31**, 473–484.

Tanabe, H., Ishida, T., Ueda, S., Sofuni, T. & Mizusawa, H. 1996 Molecular anatomy of human chromosome 9: comparative mapping of the immunoglobulin processed pseudogene Cε3 (IGHEP2) in primates. *Cytogenet. Cell Genet.* **73**, 92–96.

Thompson, P. W. & Roberts, S. H. 1987 A new variant of chromosome 16. *Hum. Genet.* **76**, 100–101.

Thomsen, P. D., Winterø, A. K. & Fredholm, M. 1998 Chromosomal assignments of 19 porcine cDNA sequences by FISH. *Mammal. Genome* **9**, 394–396.

Threadgill, D. S. & Womack, J. E. 1991 Mapping HSA 3 loci in cattle: additional support for the ancestral synteny of HSA 3 and 21. *Genomics* **8**, 1143–1148.

Threadgill, D. S., Kraus, J. P., Krawetz, S. A. & Womack, J. E. 1991 Evidence for the evolutionary origin of human chromosome 21 from comparative gene mapping in the cow and mouse. *Proc. Natl Acad. Sci. USA* **88**, 154–158.

Threadgill, D. S., Threadgill, D. W., Moll, Y. D., Weiss, J. A., Zhang, N., Davey, H. W., Wildeman, A. G. & Womack, J. E. 1994 Syntenic assignment of human chromosome 1 homologous loci in the bovine. *Genomics* **22**, 626–630.

Toder, R., Gläser, B., Schiebel, K., Wilcox, S. A., Rappold, G., Graves, J. A. M. & Schempp, W. 1997 Genes located in and near the human pseudoautosomal region are located in the X–Y pairing region in dog and sheep. *Chromosome Res.* **5**, 301–306.

Tomlinson, I. M., Cook, G. P., Carter, N. P., Elaswarapu, R., Smith, S., Walter, G., Buluwela, L., Rabbitts, T. H. & Winter, G. 1994 Human immunoglobulin V_H and D segments on chromosomes 15q11.2 and 16p11.2. *Hum. Mol. Genet.* **3**, 853–860.

Trask, B. J. (and 19 others) 1998 Members of the olfactory receptor gene family are contained in large blocks of duplicated polymorphically near the ends of human chromosomes. *Hum. Mol. Genet.* **7**, 13–26.

Van Deutekom, J. C. T., Bakker, E., Lemmers, R. J. L. F., Van der Wielen, M. J. R., Bik, E., Hofker, M. H., Padberg, G. W. & Frants, R. R. 1996 Evidence for subtelomeric exchange of 3.3 kb tandemly repeated units between chromosomes 4q35 and 10q26: implications for genetic counseling and etiology of FSHD1. *Hum. Mol. Genet.* **5**, 1997–2003.

Verma, R. S., Dosik, H. & Lubs, H. A. 1978 Size and pericentric inversion heteromorphisms of secondary constriction regions (h) of chromosomes 1, 9, and 16 as detected by CBG technique in Caucasians. *Am. J. Med. Genet.* **3**, 331–339.

Vermeesch, J. R., Petit, P., Kermouni, A., Renauld, J.-C., Van den Berghe, H. & Marynen, P. 1997 The IL-9 receptor gene, located in the Xq/Yq pseudoautosomal region, has an autosomal origin, and is expressed from the Y. *Hum. Mol. Genet.* **6**, 1–8.

Vernet, C., Boretto, J., Mattéi, M.-G., Takahashi, M., Jack, L. J. W., Mather, I. H., Rouquier, S. & Pontarotti, P. 1993 Evolutionary study of multigenic families mapping close to the human MHC class I region. *J. Mol. Evol.* **37**, 600–612.

Vine, D. T., Yarkoni, S. & Cohen, M. M. 1976 Inversion homozygosity of chromosome no. 9 in a highly inbred kindred. *Am. J. Hum. Genet.* **28**, 203–207.

Wahrman, J., Atidia, J., Goitein, R. & Cohen, T. 1972 Pericentric inversions of chromosome 9 in two families. *Cytogenetics* **11**, 132–144.

Warman, M. L., Tiller, G. E., Polumbo, P. A., Seldin, M. F., Rochells, J. M., Knoll, J. H. M., Cheng, S.-D. & Olsen, B. R. 1993 Physical and linkage mapping of the human and murine genes for the α1 chain of type IX collagen (COL9A1). *Genomics* **17**, 694–698.

Webb, T. 1994 Inv dup(15) supernumerary marker chromosomes. *J. Med. Genet.* **31**, 585–594.

Weichhold, G. M., Ohnheiser, R. & Zachau, H. G. 1993 The human immunoglobulin κ locus consists of two copies that are organized in opposite polarity. *Genomics* **16**, 503–511.

Werner, P., Raducha, M. G., Prociuk, U., Henthorn, P. S. & Patterson, D. F. 1997 Physical and linkage mapping of human chromosome 17 loci to dog chromosomes 9 and 5. *Genomics* **42**, 74–82.

White, M. J. D. 1978 *Modes of speciation*. San Francisco, CA: W. H. Freeman.

Wichman, H. A., Payne, C. T., Ryder, O. A., Hamilton, M. J., Maltbie, M. & Baker, R. J. 1991 Genomic distribution of heterochromatic sequences in equids: implications to rapid chromosomal evolution. *J. Hered.* **82**, 369–377.

Wienberg, J. & Stanyon, R. 1997 Comparative painting of mammalian chromosomes. *Curr. Opin. Genet. Dev.* **7**, 784–791.

Wienberg, J., Stanyon, R., Jauch, A. & Cremer, T. 1992 Homologies in *Macaca fuscata* chromosomes revealed by in situ hybridization with human chromosome specific DNA libraries. *Chromosoma* **101**, 265–270.

Wienberg, J., Jauch, A., Lüdecke, H.-J., Senger, G., Horsthemke, B., Claussen, U., Cremer, T., Arnold, N. & Lengauer, C. 1994 The origin of human chromosome 2 analyzed by comparative chromosome mapping with a DNA microlibrary. *Chromosome Res.* **2**, 405–410.

Wienberg, J., Stanyon, R., Nash, W. G., O'Brien, P. C. M., Yang, F., O'Brien, S. J. & Ferguson-Smith, M. A. 1997 Conservation of human vs. feline genome organization revealed by reciprocal chromosome painting. *Cytogenet. Cell Genet.* **77**, 211–217.

Wilkie, A. O. M. & Higgs, D. R. 1992 An unusually large $(CA)_n$ repeat in the region of divergence between subtelomeric alleles of human chromosome 16p. *Genomics* **13**, 81–88.

Wilkie, A. O. M., Higgs, D. R., Rack, K. A., Buckle, V. J., Spurr, N. K., Fischel-Ghodsian, N., Ceccherini, I., Brown, W. R. A. & Harris, P. C. 1990 Stable length polymorphism of up to 260 kb at the tip of the short arm of human chromosome 16. *Cell* **64**, 595–606.

Wolstenholme, J. 1995 An audit of trisomy 16 in man. *Prenatal Diagn.* **15**, 109–121.

Wong, Y. W., Williams, A. F., Kingsmore, S. F. & Seldin, M. F. 1990 Structure, expression, and genetic linkage of the mouse BCM1 (OX45 or Blast-1) antigen. Evidence for genetic duplication giving rise to the BCM1 region on mouse chromosome 1 and the CD2/LFA3 region on mouse chromosome 3. *J. Exp. Med.* **171**, 2115–2130.

Wong, Z., Royle, N. J. & Jeffreys, A. J. 1990 A novel human DNA polymorphism resulting from transfer of DNA from chromosome 6 to chromosome 16. *Genomics* **7**, 222–234.

Yang, F., Carter, N. P., Shi, L. & Ferguson-Smith, M. A. 1995 A comparative study of karyotypes of muntjacs by chromosome painting. *Chromosoma* **103**, 642–652.

Yang, F., Müller, S., Just, R., Ferguson-Smith, M. A. & Wienberg, J. 1997*a* Comparative chromosome painting in mammals: human and the Indian muntjac (*Muntiacus muntjak vaginalis*). *Genomics* **39**, 396–401.

Yang, F., O'Brien, P. C. M., Wienberg, J. & Ferguson-Smith, M. A. 1997*b* A reappraisal of the tandem fusion theory of karyotype evolution in the Indian muntjac using chromosome painting. *Chromosome Res.* **5**, 109–117.

Yang, Y.-P. & Womack, J. E. 1995 Human chromosome 17 comparative anchor loci are conserved on bovine chromosome 19. *Genomics* **27**, 293–297.

Yoo, J., Stone, R. T., Kappes, S. M. & Beattie, C. W. 1994 Linkage analysis of bovine interleukin 1 receptor types I and II (IL-1R I, II). *Mammal. Genome* **5**, 820–821.

Yunis, J. J. & Prakash, O. 1982 The origin of man: a chromosomal pictorial legacy. *Science* **215**, 1525–1530.