The Origin of Human Chromosome 1 and Its Homologs in Placental Mammals

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Developing ordered gene maps from multiple mammalian species coupled with chromosome-painting data provide a powerful resource for resolving the evolutionary history of chromosomes and whole genomes. In this work, we recapitulate the evolutionary history of human chromosome 1 and its homologs in placental mammals, putatively the largest physical unit in the ancestral placental genome. Precise definition of translocation exchange breakpoints in human, carnivore, cetartiodactyl, and rodent-ordered gene maps demonstrate that chromosome breakpoints, previously considered as equivalent, actually represent distinct chromosome positions and exchange events. Multidirectional chromosome painting, using probes from homologs to chromosome 1 in seven mammal species from six orders of placental mammals, confirm the gene-mapping results and indicate that the multiple human chromosome 1 homologs in these species are derived from independent fissions of a single ancestral chromosome. Chromosome painting using human chromosome 1 probes identifies a single human chromosome 1 homolog in phylogenetically distant taxa, the two-toed sloth, cetaceans, and higher primates. The diverse phylogenetic occurrence of a single HsaI synteny among the major clades of placental mammals suggests that human chromosome 1 represents an intact ancestral chromosome, which was variously fissioned in the majority of placental species. We find that the number of human chromosome 1 fissions in a specific lineage reflects its general rate of genomic evolution. Further, historic chromosome exchange appears to have been disproportionately clustered in two breakpoint hotspots on the long arm.

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Human chromosome 1 (Hsa1) represents the largest physical unit in the human genome, comprising some 285 million base pairs—nearly 9% of the entire genome (Lander et al. 2001, Venter et al. 2001). The genomic synteny of this chromosome is entirely conserved in apes, in some Old World monkeys (O'Brien and Stanyon 1999; Wienberg et al. 2000), and in cetaceans (Bielec et al. 1998). In the majority of other placental mammal species examined at the genomic level, Hsa1 is found as two unordered conserved segments (CSUs) in species with slower rates of genomic evolution, to as many as six CSUs in the more derived karyotypes defined by chromosome painting, such as the spider monkey and dog (Glas et al. 1998; Burt et al. 1999; O'Brien and Stanyon 1999; O'Brien et al. 1999; Breen et al. 1999; Yang et al. 2000). Because previous comparative chromosome painting results showed that Hsa1 was divided into at least two segments in nearly all species tested (>40 placental mammals from 11 orders; Wienberg et al. 2000; Murphy et al. 2001c), it was hypothesized that human chromosome 1 was originally composed of two fragments. One segment corresponds roughly to 1q21.3-pter, whereas the second segment is comprised of the remainder of the long arm (1q21.3-qter) (Chowdhary et al. 1998; Wienberg et al. 2000; Murphy et al. 2001c). Reciprocal painting of nonhuman, chromosome 1 homologs suggested a common evolutionary origin of the apportioned Hsa1 chromosomal segments in different orders. The boundary of the segments mapped repeatedly somewhere in the region 1q21–1q23 (pig: Goureau et al. 1996; cat, primate: Wienberg et al. 1997; rabbit: Korstanje et al. 1999; tree shrew: Müller at al. 1999; Fig. 1). The small differences between reports were discounted as within the margin of error when assigning hybridization signals between distantly related species (Wienberg et al. 2000).

If the two-segment ancestor hypothesis is true, then these would have fused independently in the evolutionary lineages leading to primates and cetaceans, in which a single conserved segment homologous to Hsa1 is present (Bielec et al. 1998). The alternate hypothesis would be that Hsa1 was intact in the ancestral genome of extant placental mammals. If so, then Hsa1 has been fragmented independently in the same chromosomal region in different mammalian lineages, but cannot be distinguished with the existing reciprocal chromosome-painting data. To test these competing hypotheses, we examined homologs to Hsa1 in species from nine orders of placental mammals. First, we refined the cat–human chromosome 1 comparative map and then compared these results with ordered Hsa1 comparative chromosome maps in cow, mouse, and rat species with sufficient gene density to demonstrate close, but nonidentical breakpoints. Reciprocal and multidirectional chromosome painting was performed among index species representing nine orders of placental mammals and interpreted to infer the likely ancestor of chromosome homologs of human chromosome 1. This interpretation takes into account the recent phylogenetic resolution of the 18 orders of placental mammals into four major superordinal clades (Madsen et al. 2001; Murphy et al. 2001a,b). Our results strongly suggest that the ancestral placental mammal karyotype included a single intact chromosome homologous to Hsa1. This chromosome then underwent frequent independent fission events throughout mammalian evolutionary history, but has also re-

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