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Short Communication

The complex history of distal human chromosome 1q

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Abstract

Human chromosome 1 has been claimed to be a conserved ancestral chromosome of eutherian mammals. However, two small regions from distal 1q (with orthology to mouse chromosome 11) appear to have a different history. These two regions are proposed to have been added to the ancestor of human chromosome 1 as a single block that was subsequently disrupted by a paracentric inversion. The translocation and inversion appear to have occurred at some time after the primate lineage diverged from a common ancestor with rodents. Reconstruction of the history of distal human chromosome 1q is complicated by the "reuse" of breakpoints in different mammalian lineages and by coincidental shared synteny between humans and cats.

Keywords: HSA1; SCAN domain; NALP; Comparative gene mapping

Whole-genome sequences are providing a wealth of new information about mammalian linkage groups. If a reliable phylogeny is available, these data can be used to make inferences about evolutionary changes in linkage groups. Recent phylogenetic studies [1,2] place primates together with rodents, lagomorphs, tree shrews, and flying lemurs in a clade known as Euarchontoglires. Complete genome sequences are currently available for two primates, *Pan troglodytes* and *Homo sapiens* (HSA), and two rodents, *Mus musculus* (MMU) and *Rattus norvegicus* (RNO). Euarchontoglires is the sister group to Laurasiatheria (a diverse group whose members include artiodactyls and carnivores). The best annotated laurasiatherian genome is currently that of *Canis familiaris* (CFA). Extensive sequence data are also available for *Bos taurus* (BTA) and *Sus scrofa* (SSC). Euarchontoglires and Laurasiatheria together comprise Boreoeutheria. Genomic data are limited for nonboreoeutherian mammals. *Gallus gallus* (GGA) is the only nonmammalian tetrapod for which a nearly complete genome sequence is available. These genomic data allow inferences about linkage in the genomes of three human ancestors. These are the most recent common ancestors (MRCAs) of rodents and humans, of laurasiatherians and humans, and of birds and humans.

Murphy and colleagues [3] concluded that HSA1 is a conserved linkage group that was present in the MRCA of eutherian mammals. My purpose, in this brief note, is to argue that a small region of distal HSA1q is probably a recent addition to this ancestral linkage group.

Results

The distal 100 Mb of human chromosome 1q has six breaks in synteny (A-F) between human and mouse genomes that define six blocks (I-VI) of apparently conserved synteny (Tables 1A and 1B; Fig. 1).

Breakpoints A and E

Breakpoints A and E separate genes with orthologs on MMU11 from genes with orthologs on MMU1. The genes of Blocks I and V are contiguous on MMU11 and CFA14, whereas the genes of Blocks II and VI are contiguous on MMU1 and CFA7. The simplest interpretation is that these are the breakpoints of a pericentric inversion that has occurred in either the rodent or the human lineage since both diverged from their MRCA. There are two possibilities:

(1) The current arrangement of Blocks I-VI was present in the MRCA and has been retained in the human lineage. If

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Table 1A
Flanking markers for breakpoints in human/mouse synteny from distal human chromosome 1q with chromosomal location of mouse orthologs

Breakpoint	Distal marker (mouse location)	Proximal marker (mouse location)
A	*ZNF496* (MMU11)	*ELYS* (MMU1)
B	*FMN2* (MMU1)	*CHRM3* (MMU13)
C	*ARID4B* (MMU13)	*TOMM20* (MMU8)
D	*RHOU* (MMU8)	*HIST3H2BA* (MMU11)
E	*JMJD4* (MMU11)	*CDC42BPA* (MMU1)
F	*SPTA1* (MMU1)	*CD1E* (MMU3)

so, an inversion occurred in the rodent lineage that juxtaposed Block II with Block VI and Block I with Block V. This was followed by a fission that separated (II+VI) and (I+V) onto separate rodent chromosomes.

(2) Blocks I and V were contiguous in the MRCA, as were Blocks II and VI. An inversion occurred in the human lineage to give the current human arrangement. Either Blocks (II+VI) and (I+V) were linked in the MRCA, in which case a fission occurred in the rodent lineage, or they were unlinked in the MRCA, in which case a fusion occurred in the human lineage.

I favor interpretation (2) because Blocks II and VI both contain genes that map to BTA16 and CFA7, whereas Blocks I and V contain genes mapping to BTA7 and CFA14. One of the breakpoints for this inversion would have occurred between *ZNF496* and *JMJD4* and the other between *ELYS* and *CDC42BPA* (Fig. 1). The latter breakpoint corresponds to a break in synteny between the human and the chicken genomes: the ortholog of *ELYS* maps to GGA3, whereas the ortholog of *CDC42BPA* maps to GGA14. Therefore, this short interval appears to have been involved in at least two independent evolutionary rearrangements.

Breakpoint B

Breakpoint B separates genes with orthologs on MMU13 from genes with orthologs on MMU1. *CHRM3* (ortholog on MMU13) is separated from *RGS7* (ortholog on MMU1) by 0.9 Mb on HSA1. *MACHR* and *LOC395620,* the presumed orthologs of these genes in the chicken genome, are separated by 0.3 Mb on GGA3. If the chromosome assemblies are accurate, this close juxtaposition in chickens and humans strongly suggests that *CHRM3* and *RGS7* have maintained conserved synteny since the MRCA of humans and chickens.

Table 1B
Human/mouse synteny blocks from distal human chromosome 1q

Block	MMU	Size (Mb)	Distal boundary	Proximal boundary
I	11	≈3	1q telomere	*ZNF496*
II	1	≈7	*ELYS*	*FMN2*
III	13	≈4	*CHRM3*	*ARID4B*
IV	8	≈6.5	*TOMM20*	*RHOU*
V	11	<1	*HIST3H2BA*	*JMJD4*
VI	1	≈70	*CDC42BPA*	*SPTA1*

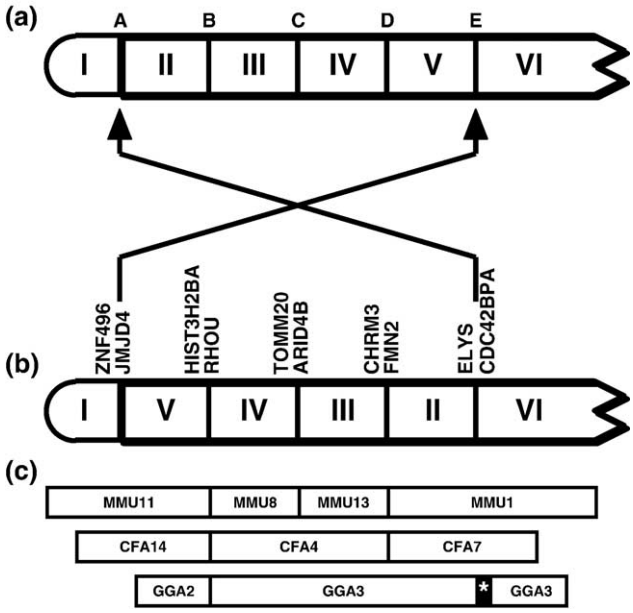

Fig. 1. Comparative gene mapping of distal HSA1q. (a) Breaks in human/mouse synteny (A-E) on HSA1 define syntenic Blocks I-VI (not drawn to scale). (b) The inferred ancestral order of these blocks in primates before the paracentric inversion that gave rise to the current gene order. (c) Syntenic relations between this ancestral order and mouse (MMU), dog (CFA), and chicken (GGA) chromosomes. The asterisk marks a small block of synteny between HSA1 and GGA14 that separates loci on HSA1 with orthologs on two noncontiguous regions of GGA3.

However, *CHRM3* and *RGS7* are unlinked in dogs, cattle, rats, and mice (*CHRM3* on CFA4, BTA28, RNO17, MMU13; *RGS7* on CFA7, BTA16, RNO13, MMU1). Since the MRCA of rodents and primates is believed to have lived more recently than the MRCA of Euarchontoglires and Laurasiatheria, conserved linkage in chickens and humans implies that there have been independent disruptions of synteny at almost identical sites in an ancestor of rats and mice and an ancestor of dogs and cattle.

Breakpoint C

Breakpoint C separates genes with orthologs on MMU13 from genes with orthologs on MMU8. Genes from Blocks III and IV, on either side of the breakpoint, have been mapped to a single bovine chromosome (BTA28), a single porcine chromosome (SSC14), and a single chicken chromosome (GGA3). Genes from both sides of the breakpoint have also been found on a single contig in *Fugu* [4]. These data strongly suggest that Blocks III and IV were linked in the MRCAs of rodents and primates, of Euarchontoglires and Laurasiatheria, and of birds and mammals. Comparative mapping between human and chicken argues strongly for this interpretation: *LYST* (on MMU13) and *IRF2BP2* (on MMU8) are separated by 1 Mb on HSA1 and the orthologous loci *LOC421514* and *LOC428585* are separated by only 140 kb on GGA3. The genes of Block IV map to RNO19, whereas the genes of Block III map to RNO17. Therefore, the disruption of conserved synteny occurred at some time in the rodent