

Variable Molecular Clocks in Hominids

Supporting Text

Tajima's non-parametric relative rate tests

Lineage specific substitutions were inferred using parsimony. In particular, if we are testing for rate difference between two species A and B with C as the outgroup and at a particular aligned site the nucleotide from A is identical to the nucleotide from C and the nucleotide from B is different, we annotate the substitution to be B lineage specific. Since the genetic distances between the ape species analyzed are extremely small, the parsimony method is apposite. This method has been used successfully in human-chimpanzee-gorilla (1) and human-chimpanzee-baboon comparisons (2). We tested whether the number of substitutions in the human lineage (N_h in Fig 2, Table 8) is significantly different from the number of substitutions in the chimpanzee lineage (N_c in Fig 2, Table 8), Tajima's non-parametric relative rate test (3).

We found that humans have accumulated significantly fewer substitutions than the chimpanzee lineage since the last human-chimpanzee common ancestor, both in introns (41070 human specific and 43214 chimpanzee specific mutations) and intergenic regions (28742 human specific and 30252 chimpanzee specific mutations) when considering the entire data set. In the high-quality data set 1 from chromosome 7 alone, humans have accumulated 1132 and 1032 fewer substitutions in introns and intergenic regions respectively. Again, the result is consistent when repetitive sequences are excluded from the alignment.

Evolution of Human Specific Life History Traits

We hypothesized that the generation time in the modern human has evolved at a certain time point since the divergence of the chimpanzee, and before that time point human and chimpanzee lineages had the same generation time. Assuming that the difference in the neutral substitution rate per year between humans and chimpanzees is caused solely by the differences in generation time, the ratios of lineage-specific branch lengths is

$$\frac{K_{OC}}{K_{OH}} = \frac{T_1}{T_2} \left/ \left(\frac{g_1}{g_2} + \frac{T_1}{T_2} - 1 \right) \right.$$

where T_1 = time since the divergence of human and chimpanzee lineages, T_2 = time since the evolution of new generation time in human lineage, g_1 = generation time in chimpanzee lineage and in ancient humans, g_2 = generation time in modern humans, and H , C , O denotes human, chimpanzee, and the common ancestor of human and chimpanzee, respectively. If we assume the generation time for chimpanzees and ancient humans is 15 years and that of the human in the recent past is 20 years ($\frac{g_1}{g_2} = 15/20 = 0.75$) and $T_1 = 7$ million years, then $T_2 \sim 10^6$ years for 3~4% slowdown in the human genome.

Correcting for Polymorphisms

The mean number of site differences between orthologous sequences from two species is equal to the mean nucleotide diversity in the ancestor population of the two species plus the

amount of differentiation after separation (4). For any two species x and y whose common ancestor is a ,

$$K_{xy} = \frac{\Pi_x}{2} + P_{ax} + \Pi_a + P_{ay} + \frac{\Pi_y}{2}$$

where K_{xy} is corrected distance between orthologous sequences from x and y (in our case, the Jukes-Cantor distance), Π_a , Π_x and Π_y are the nucleotide diversities of a , x , and y respectively and P_{ax} and P_{ay} are the number of fixed substitutions between a - x and a - y , respectively.

Using the formula used in the relative rate test (5), it is easy to show that

$$K_{oc} = P_{oc} + \frac{\Pi_o}{2} + \frac{\Pi_c}{2}$$

and

$$K_{oh} = P_{oh} + \frac{\Pi_o}{2} + \frac{\Pi_h}{2}$$

for human (h), chimpanzee (c) and the common ancestor of human and chimpanzee (o).

The difference in fixed substitutions can be measured as the ratio P_{oc}/P_{oh} , which can be calculated from K_{oc}/K_{oh} (this requires knowledge about the levels of polymorphism in current humans and chimpanzees, as well as the polymorphism of the common ancestor of humans and chimpanzees).

References

1. Ebersberger, I. & Meyer, M. (2005) *Mol Biol Evol* **22**, 1240-5.
2. Meunier, J. & Duret, L. (2004) *Mol Biol Evol* **21**, 984-90.
3. Tajima, F. (1993) *Genetics* **135**, 599-607.

4. Li, W. H. (1977) *Genetics* **85**, 331-7.
5. Wu, C. I. & Li, W. H. (1985) *Proc Natl Acad Sci U S A* **82**, 1741-5.

Figure 2. Relationship between the human-chimpanzee-baboon trio. **O** denotes the common ancestor of human and chimpanzee. The rate difference between the lineage leading to humans (OH) and the lineage leading to chimpanzees (OC) can be tested using the difference in rate between baboon-human (BH) and baboon-chimpanzee (BC). The number of substitutions in the human lineage (N_h) and the chimpanzee lineage (N_c) are inferred using parsimony.

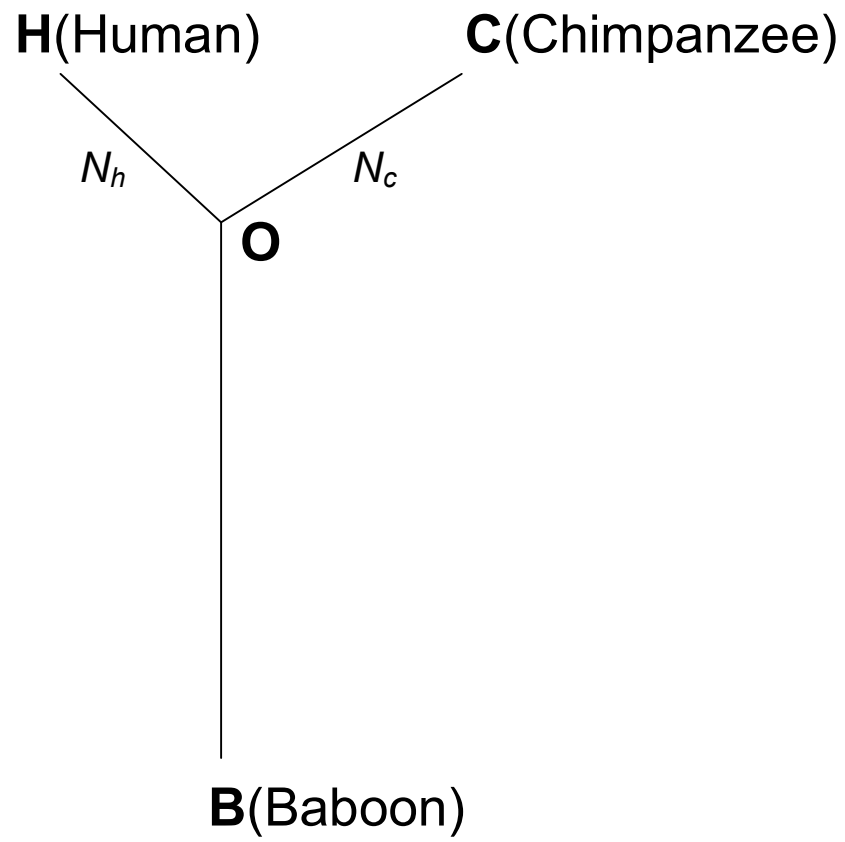


Table 5. Number of human-specific and chimpanzee-specific substitutions. High Scoring segment pairs from the intergenic regions of human chromosome 18 were less than 250 bps in length and were not included in this analysis.

Chromosome	Number of Aligned Sites	Introns		Intergenic regions		
		N_h	N_c	Number of Aligned Sites	N_h	N_c
2	41,571 (25,457)	233 (136)	266 (159)	143,774 (112,336)	783 (562)	744 (542)
4	36,539 (18,257)	219 (99)	229 (101)	55,184 (19,556)	435 (154)	474 (166)
7†	7,078,758 (4,263,620)	35226** (19879)*	36358** (20339)*	4,394,569 (2,180,898)	24048** (11342)*	25079 ** (11676) *
8†	25,135 (17,869)	134 (85)**	166 (124)**	55,151 (32,783)	476 (272)	470 (274)
10	33,533 (26,022)	202 (159)	207 (163)	91,889 (45,965)	566 (290)	620 (299)
12†	49,266 (46,909)	185** (178)**	243** (233)**	113,283 (91,873)	470** (349)**	613** (490)**
16	136,363 (68,749)	899* (364)*	992* (428)*	48,813 (16,310)	316** (91)	389** (96)
18	145,283 (121,412)	713 (539)	742 (597)	-	-	-
21†	132,603 (74,660)	982** (610)	1100** (606)	41,290 (25,445)	332** (210)**	428** (293)**
22†	443,452 (264,488)	2277** (1223)**	2911** (1607)**	214,581 (116,725)	1316* (713)	1435* (734)
Total††		41070** (23272)**	43214** (24357) **		28742** (13983)**	30252** (14570) **

†Difference between the numbers of nucleotide substitutions in human and chimpanzee lineages in introns and/or intergenic regions significant by Tajima's 1D test (Tajima 1993). * $P < 0.05$ ** $P < 0.01$

††Ratio of the numbers of nucleotide substitutions in the human and chimpanzee lineages is significantly heterogeneous among chromosomes, by the G-test of heterogeneity ($P < 0.01$).

Table 6. Different natural history traits among the hominoids studied. All the traits in the Gorilla column are of *Gorilla gorilla gorilla* except for the traits highlighted with an *, which are from *Gorilla gorilla beringei*.

Trait	Human	Chimpanzee	Gorilla	Orangutan
Infant (months)	-	60	36-48 *	48
Weaning (months)	24	48	52	42
Sexual Maturity (months)	Females: 198	Females: 135 Males: 156	Females: 78 Males: 120	Females: 84 Males: 114
Estrus Cycle (days)	28	36	32	30
Gestation (months)	9	8	8.53	8.66
Age at First Birth (months)	190 -240	168 - 180	102-132	144-196
Birth Interval (months)	10-48	60	48	96 (72-144)
Life Span (years)	80 -90	53	50	59
Mating and Birth	Year-round	Year-round Birth Peak: Oct- Nov	Year-round *	Year-round
Social Structure	Variable. 1 male - 1 female monogamous pairs and 1 male-multifemale family groups are the most common.	Multimale-multifemale, fission fusion community. Related males patrol the territory. Females are solitary. Males are dominant	One or two males and many females in a group.	Males are solitary. Females travel with their offspring
Emigration	Both males and females emigrate	Females emigrate to other communities	Both males and females emigrate.	-
Group Size	Variable	7-25 males, 5-16 females. Up to 100.	3-21	1-3

Mating	Variable	Promiscuous mating is common	Females initiate	Females initiate
Height (mm)	Females: 1370-1774 Males: 1450-1816	816 (737-959)	Females: 1500 Males: 1700	Females:780 Males:970
Weight (Kg)	Females: 55 (37- 76.6) Males: 68.23 (43-76)	Females: 32 – 47 Males: 40 - 60	Females: 71.5 Males: 169.5	Females: 33-45 Males: 77.5
Intermembral Index	72	103-106	115.6	139
Adult Brain Weight (g)	1250	410.3	505.9	413.3

Table 7. Data set1: Regions in the human chromosome 7 (from NCBI Build 35) analyzed using high-quality BAC based sequence data from orthologous regions in chimpanzee and baboon.

	Positions in Human Chromosome 7 (start – end)	Approximate Size (Mb)
Fragment 1	115404472 - 117281897	1.88
Fragment 2	124767156 - 128790277	4.02
Fragment 3	27335605 - 32242686	4.91
Fragment 4	89255894 - 95853584	6.60
Fragment 5	72172417 - 75806932	3.63
Fragment 6	101051374 - 101877969	0.83
	Total	21.87

Table 8. Data set2: Data mined from GenBank for human-chimpanzee-baboon alignments.

Baboon BAC clone GI	Length of Baboon BAC Clone	Human Contig	Human Chromosome	Chimpanzee Chromosome
19852149	176,602	NT_005403	2	13
20531803	183,807	NT_005120	2	13
37777362	179,810	NT_077444	4	3
40018755	188,182	NT_023736	8	7
47901706	162,030	NT_077531	8	7
22038600	180,097	NT_033985	10	8
27884981	208,592	NT_029419	12	10
20514788	183,586	NT_010393	16	18
34849945	189,610	NT_010393	16	18
48210289	184,931	NT_010393	16	18
27877209	154,605	NT_025028	18	17
46092384	183,435	NT_011515	21	22
46092385	178,968	NT_011515	21	22
21070693	182,747	NT_011520	22	23
25704382	157,944	NT_011519	22	23
26080536	173,331	NT_011520	22	23
28376744	202,399	NT_011519	22	23
28850065	186,148	NT_011520	22	23
33342323	177,987	NT_011520	22	23
33342325	186,113	NT_011520	22	23
34849943	169,197	NT_011519	22	23
34849944	172,406	NT_011519	22	23
Total	3,962,527			

Table 9. Human Chromosome 21 region aligned to Rhesus scaffolds.

Chain #	Human Chromosome 21 Matching Region				Rhesus Scaffolds				
	Start	End	Length	Scaffold Name	Matching Regions to Human				
					Scaffold Length	Start	End	Strand	Length
1	14420137	14691875	271738	SCAFFOLD90025	256051	2	250516	+	250514
2	15370334	15492255	121921	SCAFFOLD60191	125283	322	125281	-	124959
3	15755850	15855861	100011	SCAFFOLD75310	101234	2	101232	-	101230
4	16008840	16273303	264463	SCAFFOLD95054	263993	321	263991	-	263670
5	16478042	16735191	257149	SCAFFOLD25001	362421	4	358588	+	358584
6	18007221	18116006	108785	SCAFFOLD25407	118702	5723	118698	-	112975
7	18247583	18559583	312000	SCAFFOLD50012	312202	2	312199	-	312197
8	18559501	18660469	100968	SCAFFOLD70567	100011	2	100009	+	100007
9	18699670	18834512	134842	SCAFFOLD5110	136072	2	136067	+	136065
10	18870891	19005460	134569	SCAFFOLD60115	148722	2518	148720	-	146202
11	19204579	19331946	127367	SCAFFOLD120124	132750	2	132748	+	132746
12	19702071	19870967	168896	SCAFFOLD120169	139350	2	139348	-	139346
13	19931075	20085117	154042	SCAFFOLD110065	162929	2	162927	-	162925
14	20085627	20192795	107168	SCAFFOLD100205	106692	7	106690	-	106683
15	20570287	20742322	172035	SCAFFOLD5114	165533	14	165531	-	165517
16	21170208	21271964	101756	SCAFFOLD95363	104431	292	102398	+	102106
17	21480291	21590811	110520	SCAFFOLD75154	124157	1621	124155	+	122534
18	21685626	22010246	324620	SCAFFOLD95033	320530	858	320528	+	319670
19	22593873	22813714	219841	SCAFFOLD15029	250248	2	250215	-	250213
20	22968174	23141099	172925	SCAFFOLD55018	207494	2	207492	+	207490
21	23204923	23364619	159696	SCAFFOLD90148	138984	2	136583	+	136581
22	24513380	24638469	125089	SCAFFOLD40193	134684	13	134682	-	134669
23	24955038	25064766	109728	SCAFFOLD85147	116982	2	116712	+	116710
24	25229434	25334479	105045	SCAFFOLD60196	104403	2	104235	-	104233
25	25532155	25646489	114334	SCAFFOLD144	120917	400	119565	+	119165
26	25653613	25768950	115337	SCAFFOLD20099	132456	399	132454	+	132055
27	25996354	26164273	167919	SCAFFOLD50104	176311	2	176309	-	176307

28	26484374	26654145	169771	SCAFFOLD10167	163283	2	163281	-	163279	
29	26654695	26814610	159915	SCAFFOLD85277	162968	2	162897	+	162895	
30	26814935	27062437	247502	SCAFFOLD120107	152560	2	152554	-	152552	
31	27112378	27401854	289476	SCAFFOLD36	281468	2	281466	-	281464	
32	27441127	27571178	130051	SCAFFOLD35173	141368	2	141366	+	141364	
33	27798871	28090767	291896	SCAFFOLD40008	263240	2	263238	-	263236	
34	29153254	29240176	86922	SCAFFOLD60492	103209	2	103199	+	103197	
35	29931319	30334616	403297	SCAFFOLD5003	409599	2	409597	-	409595	
36	30350057	30502373	152316	SCAFFOLD30104	145075	2	145073	+	145071	
37	30503122	30660579	157457	SCAFFOLD85153	174432	2	174430	-	174428	
38	31922963	32050947	127984	SCAFFOLD55201	126002	1921	125999	+	124078	
39	32579126	32721389	142263	SCAFFOLD20175	143704	340	143702	+	143362	
40	34761533	34994963	233430	SCAFFOLD95135	220876	2	220357	-	220355	
41	35288970	35475114	186144	SCAFFOLD115229	184058	9	184056	+	184047	
42	35526751	35774503	247752	SCAFFOLD80014	249012	2	248682	+	248680	
43	35812819	36002949	190130	SCAFFOLD30065	190634	2	190632	-	190630	
44	36130379	36283771	153392	SCAFFOLD10127	154932	2	154930	+	154928	
45	36809821	36997270	187449	SCAFFOLD65230	171703	2	171701	+	171699	
46	37378588	37505041	126453	SCAFFOLD20171	116270	2	116268	+	116266	
47	38212661	38353450	140789	SCAFFOLD65121	138768	2	138764	+	138762	
48	38454472	38630865	176393	SCAFFOLD105100	169513	321	169509	-	169188	
49	39051606	39195956	144350	SCAFFOLD25181	141438	922	141436	+	140514	
50	39309575	39513236	203661	SCAFFOLD85087	196523	2	196518	-	196516	
51	39934055	40112408	178353	SCAFFOLD35068	166788	2	166784	-	166782	
52	40544739	40668487	123748	SCAFFOLD100317	116184	2	116180	-	116178	
53	40690435	40977544	287109	SCAFFOLD100104	291593	3	291591	-	291588	
54	41124818	41280243	155425	SCAFFOLD75125	145846	2	141822	-	141820	
55	41289273	41433451	144178	SCAFFOLD55107	158471	2	158111	-	158109	
56	41518412	41639915	121503	SCAFFOLD10229	126760	2	126755	-	126753	
57	41965944	42080241	114297	SCAFFOLD85122	116185	2	115139	-	115137	
58	42477617	42644790	167173	SCAFFOLD45333	164190	2	164188	-	164186	
Total				10003343					Total	10012012