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Evolutionary Rate Acceleration of Cytochrome *c* Oxidase Subunit I in Simian Primates

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Abstract. We present an analysis of the evolutionary rates of the cytochrome *c* oxidase subunit I genes of primates and other mammals. Five primate genes were sequenced, and this information was combined with published data from other species. The sequences from simian primates show approximately twofold increases in their nonsynonymous substitution rate compared to those from other primates and other mammals. The species range and the overall magnitude of this rate increase are similar to those previously identified for the cytochrome *c* oxidase subunit II and cytochrome *b* genes.

Key words: Relative rates test — Electron transport chain — Mitochondria — Cytochrome — Simian primates — Positive selection — Maximum likelihood — Base compositional heterogeneity

Introduction

A number of the protein components of the electron transport chain (ETC) in simian primates exhibit accelerated evolutionary rates compared with those in other mammals, including nonsimian primates. The cytochrome *b* (Andrews et al. 1998) and cytochrome *c* oxidase subunit II (COII) (Adkins and Honeycutt 1994; Adkins et al. 1996) genes, both encoded in the mitochondrial genome, demonstrate an approximately twofold increase in their nonsynonymous substitution rate in simian primate species compared to other primate and nonprimate mammals. Such increases in nonsynonymous evolutionary rate have prompted the suggestion that these genes have undergone positive selection in simian primates (Andrews et al. 1998) and may imply that an episode of adaptive change has occurred to the ETC in these species. Such a possibility is lent further support by the finding that a number of nuclear-encoded components of the electron transport chain also show rate anomalies that could be related to rate accelerations among the mitochondrial genes. Nuclear-encoded cytochrome *c* appears to have undergone a period of rapid evolution of the lineage leading to humans, and by extrapolation, potentially a similar rate increase may have occurred in other primates (Baba et al. 1981; Evans and Scarpulla 1988). More recent analysis of nuclear-encoded components of the cytochrome *c* oxidase complex has also revealed that at least three of these subunits have undergone nonsynonymous rate accelerations in primates (subunits IV, VIa, and VIIa), and in two cases (subunits IV and VIIa) these rate increases could be attributed to nonneutral evolution (Wu et al. 1997; Schmidt et al. 1997, 1999).

Cytochrome *c*, COII, and cytochrome *b* are closely related functionally, in that they operate in concert as components of the ETC. Cytochrome *b* and COII are key subunits of the final two complexes (III and IV) of the

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ETC. Cytochrome *c* interacts with both of these complexes in its action of transporting electrons from complex III to complex IV (Hatefi 1985). It has been shown that the reaction of simian cytochrome *c* with simian complex IV (of which COII forms the cytochrome *c* binding site) is different in protein–protein binding character from that of other mammals (Osheroff et al. 1983). This information viewed collectively with the information on rate variation in these genes has led to speculation that these mitochondrial components may have coevolved (Cann et al. 1984; Andrews et al. 1998).

From an analysis of nucleotide substitution rates across mammals in fully sequenced mitochondrial genomes, Janke et al. (1994) showed that a number of mitochondrial encoded genes violated an assumption of a uniform or "clock-like" evolutionary rate. These genes were shown to include, in decreasing degree of rate violation, the COII, cytochrome *b*, and cytochrome *c* oxidase subunit I (COI) genes. The recently solved crystal structure of the bovine heart cytochrome *c* oxidase complex (Tsukihara et al. 1996) shows that COI binds to COII and transduces electrons passed to it from cytochrome *c*. Potentially, an episode of coordinated adaptive evolution that involved COII, cytochrome *b*, cytochrome *c*, and at least two nuclear-encoded subunits of cytochrome *c* oxidase could also involve COI.

This paper presents new COI nucleotide sequences from five primate species along with a comparative investigation of the evolutionary rate of this gene in simian primates and other mammals.

Materials and Methods

DNA Sources and Sequencing. Liver samples from *Hapalemur griseus* (gray-gentle lemur) and *Galago senegalensis* (lesser bushbaby) and a lung sample from *Tarsius bancanus* (Bornean tarsier) were obtained from the Duke University Primate Center. Blood plasma samples from *Ateles geoffroyi* (spider monkey) and *Colobus polykomos* (black-and-white colobus) were donated by the Royal Melbourne Zoological Gardens. DNA was phenol/chloroform extracted from either whole-plasma samples or homogenates of tissue samples using standard protocols (Sambrook et al. 1989). The COI gene was isolated from each species using the polymerase chain reaction (PCR) with the "universal" oligonucleotide primers shown in Table 1. Nucleotide sequences of both strands of each gene were determined directly from the PCR product using dye-terminator cycle sequencing (Perkin) with the original PCR primers and additional internal sequencing primers (Table 1) on an ABI377 automated sequencer (Applied Biosystems). Additional COI sequences were obtained from published sources: *Balaenoptera physalus* [fin whale; X61145] (Arnason et al. 1991), *Felis catus* [domestic cat; U20753] (Lopez et al. 1996), *Homo sapiens* [human; J01415] (Anderson et al. 1981), and *Mus musculus* [mouse; J01420] (Bibb et al. 1981). COII sequences were also obtained from previously published sources: *Alouatta palliata* [mantled red howler monkey; L22774], *Tarsius bancanus* [Bornean tarsier; L22783], *Galago senegalensis* [lesser bushbaby; M80905], *Lemur catta* [ring-tail lemur; L22780] (Adkins and Honeycutt 1994), *Macaca mulatta* [rhesus macaque; M74005] (Disotell et al. 1992), *Balaenoptera physalus* [fin whale; X61145] (Arnason et al. 1991), *Felis catus* [domestic cat; U20753] (Lopez et al. 1996), *Homo sapiens* [human; J01415] (Anderson et al. 1981), and *Mus musculus* [mouse; J01420] (Bibb et al. 1981).

Table 1. Oligonucleotide primers used in the amplification and sequencing of COI genes

Primer[a]	Sequence (5′–3′)[b]
"Universal" primers[c]	
H5783	GGCTICTTIGAATTTGCAATTCIA
L7453	TGIGGGTTCGATTCCTTCCTT
Ateles geoffroyi	
H6179	TAGCATTTCCACGAATGAATAA
H6532	CTGACTGACCGTAATCTTAA
H6903	ATGATCTCCTGCAATGCTAT
H7225	TCAGATTACCCCGATGCAT
L7085	AATAGTGGGAAICAGTGAA
L6636	TCCAGGGAGRATAAGGATA
L6283	CTAAGGGTGGGTAAACTGT
Colobus polykomos	
H6171	CCCTGACATAGCATTICC
H6644	TTTTACCAGGCTTTGAATAA
H6881	CACTTCACGGACGCAATAT
H7228	GACTACCCCGACGCTTA
L7100	TTAGAGTATAGCCTGAGAATA
L6804	AAGTGAAATAGGCTCGTGTA
L6324	GGTTAAGTCTACAGAGGCT
Hapalemur griseus	
H6197	ACAACATGAGCTTCTGACT
H6597	TCAACACCTATTCTGATTCTT
H6878	CGACATTACATGGTGGCAA
H7225	TCTGACTATCCAGATGCCT
L7065	GGACGAAICCICCTATAAT
L6700	CCTATATAACCRAATGGTTC
L6287	CCTGCTAGAGGAGGATATA
Galago senegalensis	
H6271	GGGACCGGATGAACCGT
H6667	CCACATCGTATCCTATTACT
H6973	GTCTTATCAAACTCCTCGTT
L7204	ACGACGAGGCATACCTGA
L6715	TTATTGCCCAGACTATTCCT
L6353	GATACTCCTGCTAGGTGAA
Tarsius bancanus	
H6179	TAGCATTYCCTCGAATAAATAA
H6747	CTTCTTAGGTTTCATTGTCTG
H7080	CTTCGTTCACTGATTCCCA
H7227	CGACTACCCTGACGCATA
L7033	AATAGTGGGAAICAGTGAA
L6636	as above
L6173	TTCGAGGGAATGCTATATCA

[a] Primer numbers refer to the nucleotide at the 5′-most end of the sequence and are numbered with reference to the scheme of Anderson et al. (1981). H and L refer to the strand to which the primer anneals.
[b] I represents deoxyinosine; degenerate bases are represented by standard notation.
[c] Universal primers were used for the first sequencing steps from both ends of all genes.

Data Analysis. The base composition of each COI gene was determined using the EComposition program of the GCG package (Genetics Computer Group, Wisconsin) available via the Australian National Genomic Information Service (www.angis.org.au).

Base compositional heterogeneity among the COI sequences was assessed using the program, Distance, by L.S. Jermiin. Pairwise *Z* scores were calculated between all pairs of nucleotide sequences at each codon position, and the magnitude and range of these graphed to determine which codon sites showed the least compositional heterogeneity (see description in Andrews et al. 1998).

Inferred COI and COII amino acid sequences were aligned using CLUSTAL W (Thompson et al. 1994) and did not require the insertion

Table 2. Base compositions of COI genes at each codon position

	First codon position				Second codon position				Third codon position			
Species	% A	% T	% G	% C	% A	% T	% G	% C	% A	% T	% G	% C
Human	26.3	22.4	28.8	23.4	19.1	40.5	14.6	25.7	36.0	16.9	5.1	41.8
Colobus	26.7	24.5	27.8	21.0	18.7	41.4	14.6	25.1	35.0	26.7	5.3	32.9
Spider monkey	27.0	23.5	27.8	21.6	18.9	40.5	14.4	26.1	38.3	27.2	4.7	29.6
Tarsier	26.1	23.3	29.0	21.6	17.9	40.7	14.8	26.5	38.7	27.6	2.9	30.5
Hapalemur	26.3	25.5	30.0	18.3	18.5	40.5	14.8	26.1	40.7	32.1	4.7	22.4
Galago	26.3	24.5	29.2	20.0	17.9	40.9	14.8	26.3	38.1	27.6	6.4	27.6
Whale	27.0	23.7	29.0	20.0	17.9	40.9	15.0	26.1	40.9	21.4	4.7	32.9
Cat	26.7	24.7	29.2	19.5	18.1	40.9	14.8	26.1	34.8	29.2	10.1	25.7
Mouse	25.9	24.1	29.8	20.4	18.3	40.5	14.8	27.7	44.4	27.4	4.1	24.3

of gaps. Hence, the COI and COII nucleotide sequences were also aligned without gaps.

Uniformity of evolutionary rates among nucleotide sequences was tested using the relative rates test of Muse and Weir (1992). Additional relative rates tests were conducted using substitution rates estimated by the method of Wu and Li (1985), and *Z* statistics for these tests were calculated as described by Muse and Weir (1992). Where Jukes–Cantor corrected distances (1969) have been used to conduct relative rate tests, the variance of K_{13}–K_{23} was computed as described by Nei et al. (1985), using the method of Kimura and Ohta (1972) to calculate Var(*K*).

Ancestral COI amino acid sequences were estimated with the maximum-likelihood method of Yang et al. (1995) using the codeml program of the PAML package [Version 1.3c (Yang 1997)].

Results

Primate COI Genes

New primate COI nucleotide sequences were obtained for *Ateles geoffroyi*, *Colobus polykomos*, *Galago senegalensis*, *Hapalemur griseus*, and *Tarsius bancanus* (DDBJ/GenBank/EMBL database accession numbers AB016730–AB016734). These five genes exhibit high levels of similarity among themselves and with other previously published mammalian sequences. The new nonsimian COI nucleotide sequences are 1512 base pairs long and translate to a protein of 513 amino acids, the same length as the human sequence. The sequences obtained for the colobus and spider monkey are longer than the human and the other sequences at their 3′ end, by one and five codons, respectively. The extra codons and putative termination codon for the spider monkey sequence intrude well into the downstream serine-tRNA gene, and instead this gene is probably posttranscriptionally terminated by the addition of a poly(A) tail, as are many mitochondrial genes (Anderson et al. 1981, 1982). Fixation of a poly(A) tail following thymine at position 1542 of the spider monkey gene forms a termination codon, and termination here makes the spider monkey and human proteins the same size.

Base Composition

The COI genes were examined at the first, second, and third codon positions for possible base compositional differences (Table 2). Visual inspection of the table indicates that the third codon positions are more compositionally heterogeneous than the first and second codon positions. To analyze this difference in base composition further, pairwise comparisons between sequences were conducted to test the compositional uniformity of each pair of sequences. Figure 1 shows the frequency distribution of *Z* statistics for comparisons at each codon position. The compositional heterogeneity present at third codon positions, evidenced by the larger range and magnitude of *Z* values, makes these data a poor source of information for analysis of substitution rates. Hence, in the following analyses, where it is appropriate, third codon positions have been excluded.

Phylogenetic Assumptions

Previous analyses of the cytochrome *b* and COII genes from simian primates showed that these genes do not adequately resolve the expected phylogenetic relationships (Adkins and Honeycutt, 1994; Andrews et al. 1998). This was also the case for the COI sequences (data not shown). In the following analyses, general primate phylogenetic relationships implicitly required for the correct application of relative rate tests were derived from Groves (1989) and Irwin et al. (1991).

Relative Rates of Evolution

Two kinds of relative rates test were employed to test the hypothesis that there is an increase in the evolutionary rate of simian COI genes compared to those of other mammals.

First, evolutionary rates of COI sequences were compared using the likelihood-ratio test of Muse and Weir (1992). Briefly, multiple log-likelihood scores were generated for groups of three sequences (two ingroups and their outgroups). Each score was calculated using a substitution model that assumed equal substitution rates between the genes of different species, and this was compared with the log-likelihood score calculated using a model that allowed substitution rates to vary between

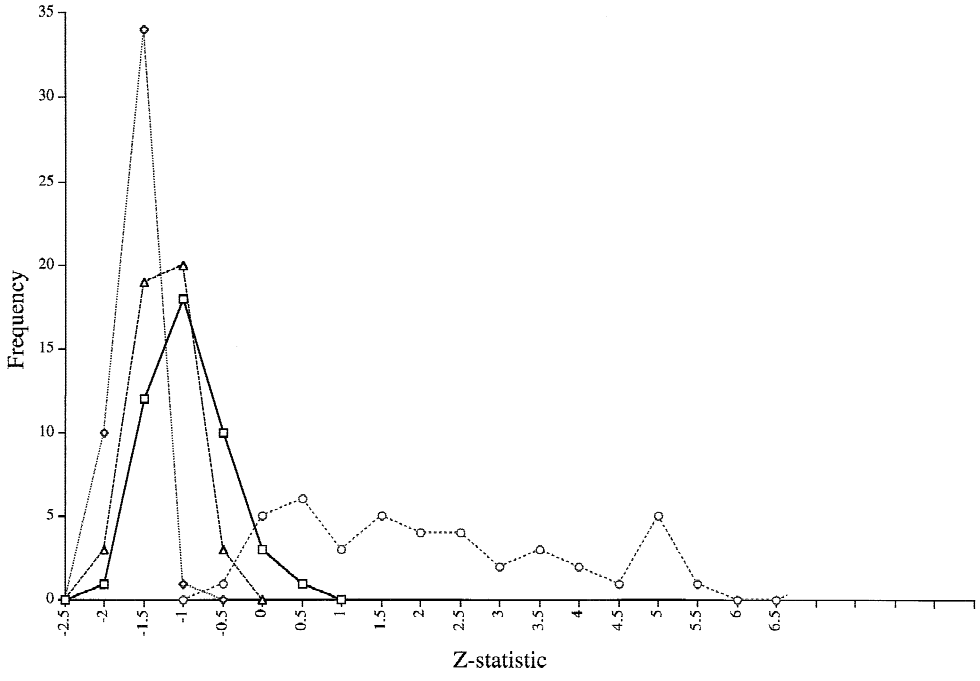

Fig. 1. Frequency distribution of COI base composition heterogeneity measured as pairwise *Z* statistics. First codon position *Z*-statistic frequencies are represented by *squares*, second codon positions as *diamonds*, third codon positions as *circles*, and first and second positions combined as *triangles.*

lineages. The log-likelihood ratios calculated from these comparisons were tested for significance against a χ^2 distribution with 2 degrees of freedom. Only first and second codon positions were used for these tests. The results do not indicate the direction of any rate variation detected.

Second, the method of Wu and Li (1985) was used. This method treats substitutions differently depending on whether they occur at nondegenerate, twofold degenerate, or fourfold degenerate sites. The method allowed for the direction of any difference in substitution rate to be identified. Furthermore, the division of sites into degeneracy classes allowed an unbiased estimate of synonymous substitutions to be made. This can be obtained from transversion substitutions at fourfold degenerate sites, since there is no indication of base compositional heterogeneity at fourfold degenerate sites when bases are combined into purine and pyrimidine classes.

There is a high degree of consistency between the results obtained using these two methods (Table 3). Both methods indicate a lack of rate difference between galagos and tarsiers using cats as an outgroup, and both indicate rate differences between simians and galagos/tarsiers using cats/galagos as outgroups. Both methods indicate relative rate uniformity between platyrrhines and catarrhines and a rate difference between Old World monkeys and humans. The difference between simian and nonsimian primates is due to an approximately two- to threefold elevation of substitution rate in simians.

The phylogenetic range and the magnitude and direction of the evolutionary rate acceleration are thus the same for COI as they are for COII and cytochrome *b.*

Discussion

Previous investigations of the evolutionary rates of primate mitochondrial genes have shown that the cytochrome *b* (Andrews et al. 1998) and COII (Adkins and Honeycutt 1994) genes have increased rates of nonsynonymous substitution in simian primates. The analysis conducted here presents further evidence that these rate increases may be part of a multienzyme evolutionary phenomenon and had shown that COI sequences from simian primates have undergone an evolutionary rate acceleration in the same species range as both the cytochrome *b* and the COII genes. Each of these three mitochondrial genes shows a rate acceleration in simian primates of approximately the same magnitude, being about a two- to threefold increase in nonsynonymous substitution rates compared to that of other closely related mammals. These increases in evolutionary rate also appear not to be uniform among the simian primates—for each gene the Old World monkeys (baboons, macaques, colobine monkeys) show the greatest increase in substitution rate.

The evidence does not rule out a relaxation of functional constraint as a driving force for the rate accelerations observed. However, given that the ETC is a vital system for all respiring cells, it is unlikely that whole parts of this pathway could become either fully or partially functionally unconstrained. Hence it is of interest to consider other possibilities—one of these is that functional changes have taken place in the simian ETC proteins and that these have been subjected to positive selection. Biochemical differences between the simian

Table 3. Rate variation between COI sequences assessed

Outgroup (3)	Species (1)	Species (2)	Muse and Weir (1992) method[a]	Wu and Li (1985) method[b]					
				Nondegenerate subsitutions			Fourfold degenerate transversions		
				$K_{12} \pm$ SE	K_{13}–$K_{23} \pm$ SE	K_{02}:K_{01}[c]	$B_{12} \pm$ SE	B_{13}–$B_{23} \pm$ SE	B_{02}:B_{01}[c]
Cat	Galago	Hapalemur	4.51	2.83 ± 0.5	0.35 ± 0.69	0.752	101.7 ± 23.2	20.2 ± 34.2	0.777
		Tarsier	1.98	2.77 ± 0.5	0.20 ± 0.69	0.737	56.6 ± 8.9	6.6 ± 35.8	0.306
		Spider monkey	4.35	5.94 ± 0.8	−2.14 ± 0.88	3.01	151.2 ± 62.5	18.9 ± 35.2	2.34
		Colobus	16.30*	7.10 ± 0.8	−3.67 ± 0.97	3.53	123.2 ± 35.9	20.5 ± 34.6	1.24
		Human	8.14	5.36 ± 0.8	−2.04 ± 0.86	2.34	84.6 ± 17.0[d]	3.7 ± 37.5[d]	4.56[d]
Galago	Tarsier	Spider monkey	13.61*	4.76 ± 0.7	−3.16 ± 0.85	2.00	91.5 ± 18.6	−94.6 ± 62.7	1.60
		Colobus	20.78*	6.45 ± 0.8	−4.32 ± 0.94	3.14	134.8 ± 45.2	−66.6 ± 37.0	4.47
		Human	9.64*	5.10 ± 0.7	−2.58 ± 0.84	2.53	92.1 ± 18.8	−39.5 ± 17.6[d]	0.915[d]
Tarsier	Spider monkey	Human	0.06	4.66 ± 0.7	−0.34 ± 0.89	0.962	44.0 ± 6.6	−0.68 ± 23.6	0.319
	Colobus	Human	0.84	6.09 ± 0.8	1.35 ± 0.98	0.868	30.8 ± 4.8	42.7 ± 44.2	0.060
	Colobus	Spider monkey	0.74	7.66 ± 0.9	1.69 ± 1.01	1.68	63.2 ± 10.4	43.4 ± 46.6	0.121
Spider monkey	Colobus	Human	11.47*	6.09 ± 0.8	3.00 ± 1.01	0.496	30.8 ± 4.8	19.2 ± 10.9	0.153

[a] Asterisks denote significance at a confidence level of $\alpha = 0.05$ assuming that the data resembles a χ^2 distribution with 2 degrees of freedom.
[b] Per 100 sites.
[c] $K_{01} = (K_{13} + K_{12} - K_{23})/2$, $K_{02} = (K_{12} + K_{23} - K_{13})/2$, $B_{01} = (B_{13} + B_{12} - B_{23})/2$, and $B_{02} = (B_{12} + B_{23} - B_{13})/2$.
[d] The pairwise comparison of the galago and human sequences at fourfold degenerate transversion sites resulted in a division by zero error in the calculation of the value of Q (see Wu and Li 1985), and hence Jukes–Cantor (1969) corrected values are shown instead.

ETC and that of other mammals have now been known for over a decade. It has been shown that the cytochrome *c* proteins from a large range of mammals are interchangeable with cytochrome *c* oxidase from other species—except with simian primates. The reaction of simian cytochrome *c* with cytochrome *c* oxidase from other nonsimian mammals proceeds with a greatly reduced V_{max} (Osheroff et al. 1983). Present information derived from the more recent sequencing of the genes from the simian primate ETC and the solved crystal structure of the cytochrome *c* oxidase complex (Tsukihara et al. 1996) allow structural analysis of possible reasons for this enzymatic difference. Simian-specific amino acid changes to the COI and COII genes were determined through ancestral reconstructions (data not shown) and these changes superimposed on a stripped-down two-subunit model of cytochrome *c* oxidase derived from the crystal structure (Fig. 2). Most of the simian-specific amino acid changes were found to be conservative and are likely to be neutral. However, in the region of the cytochrome *c* oxidase complex believed to be responsible for cytochrome *c* binding (the intermembrane space-side extramembrane loop of COII; see Fig. 2), there was a concentration of changes that very possibly could influence the nature of protein–protein interactions. Cytochrome *c* binding to cytochrome *c* oxidase is thought to be mediated by interactions between positively charged residues on cytochrome *c* and a patch of negatively charged glutamates and aspartates on COII (Lappalanien et al. 1995; Witt et al. 1998). On the lineage leading to simian primates, two changes (D127F and E157Q) remove negatively charged residues from the edges of the region where cytochrome *c* may bind. This loss of negative residues may be compensated for the replacement of a positive with a negative residue at position 129 (K → E) in some simians (apes and Old World monkeys; in New World monkeys the change is K → N, which just removes the positive change). Potentially, the removal or shuffling of these charged residues in simian primates may partially explain the functional divergence of this interaction from that observed in other mammals.

In addition to the evolutionary rate accelerations seen for the mitochondrial encoded subunits, three nuclear-encoded components of cytochrome *c* oxidase display high nonsynonymous substitution rates in primate species (with the greatest nonsynonymous rates evident along catarrhine lineages) (Wu et al. 1997; Schmidt et al. 1997, 1999). It is not obvious whether these events are related to evolutionary changes that have occurred among the mitochondrial-encoded subunits. In the case of COVIa (Schmidt et al. 1997) and COVIIa (Schmidt et al. 1999), it appears that changes to these subunits are related to the evolution of tissue specificity of these subunits (divergence of heart and liver isoforms) following gene duplication. The three nuclear-encoded subunits so far analyzed have each come into physical contact with either COI or COII, and hence it is possible that the unusual evolutionary rates of these subunits may be related to the seemingly coordinated evolution if cytochrome *b*, cytochrome *c*, COI, and COII. Potentially, some of the seven other nuclear-encoded subunits of cytochrome *c* could also be involved and may display elevated rates of nonsynonymous evolution in simian primates. Clearly, further investigation of the nuclear-encoded subunits of cytochrome *c* oxidase would be valuable.

From the body of work that has now accumulated on

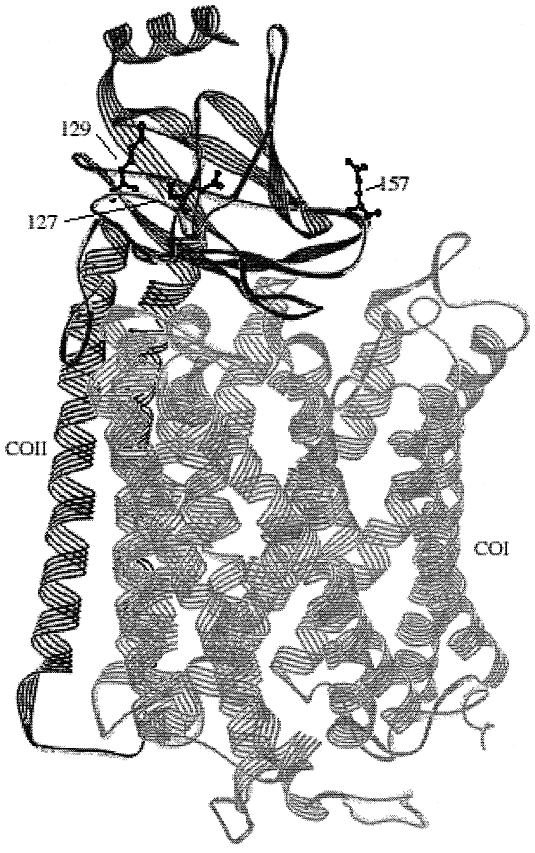

Fig. 2. A stripped-down structure of cow cytochrome *c* oxidase consisting only of COI (*light gray*) and COII (*dark gray*). Important changes inferred from reconstructed ancestral sequences are indicated by residue numbers.

the evolution of the ETC in simian primates, it is becoming apparent that whatever has happened, a large number of functionally related protein subunits have undergone a coordinated (or at least highly coincidental) evolutionary change. Comparative investigation of the evolutionary rates of other subunits in complexes III and IV of the ETC may allow a definition of the range of proteins that have symmetrical evolutionary histories. Certainly, detailed analysis of the recent evolution of cytochrome *c* in simian primates will provide important information. Furthermore, comparative biochemical study is also needed to determine if the rate accelerations so far identified have any meaning at a functional level. Site-directed mutagenesis experiments focusing on important changes in simian proteins (especially in COII) will be important in determining if the accelerated evolution observed in simian ETC genes could have been driven by positive selection. Conducting site-directed mutagenesis experiments on mitochondrial genes would be a technically demanding process, and potentially the use of the *Parracoccus* model system coupled with in silico modeling would be a much more feasible approach.

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References

Adkins RM, Honeycutt RL (1994) Evolution of the primate cytochrome *c* oxidase subunit II gene. J Mol Evol 38:215–231

Adkins RM, Honeycutt RL, Disotell TR (1996) Evolution of eutherian cytochrome *c* oxidase subunit II: Heterogeneous rates of protein evolution and altered interaction with cytochrome *c*. Mol Biol Evol 13:1394–1404

Anderson S, Bankier AT, Barrell BG, de Bruijn MHL, Coulson AR, Drouin J, Eperon IC, Nierlich DP, Roe BA, Sanger F, Schreier PH, Smith AJH, Staden R, Young IG (1981) Sequence and organisation of the human mitochondrial genome. Nature 290:457–465

Anderson S, de Bruijn MH, Coulson AR, Eperon IC, Sanger F, Young IG (1982) Complete sequence of bovine mitochondrial DNA. Conserved features of the mammalian mitochondrial genome. J Mol Biol 156:683–717

Andrews TD, Jermiin LS, Easteal S (1998) Accelerated evolution of cytochrome *b* in simian primates: Adaptive evolution in concert with other mitochondrial proteins? J Mol Evol 47:249–257

Arnason U, Gullberg A, Widegren B (1991) The complete nucleotide sequence of the mitochondrial DNA of the fin whale, *Balenoptera physalus.* J Mol Evol 33:556–568

Baba ML, Darga LL, Goodman M, Czelusniak J (1981) Evolution of cytochrome *c* investigated by the maximum parsimony method. J Mol Evol 17:197–213

Bibb MJ, Van Etten RA, Wright CT, Walberg MW, Clayton DA (1981) Sequence and gene organisation of mouse mitochondrial DNA. Cell 26:167–180

Cann RL, Brown WM, Wilson AC (1984) Polymorphic sites and the mechanism of evolution in human mitochondrial DNA. Genetics 106:479–499

Disotell TR, Honeycutt RL, Ruvolo M (1992) Mitochondrial DNA phylogeny of the Old-World monkey tribe *Papionini*. Mol Biol Evol 9:1–13

Evans MJ, Scarpulla RC (1988) The human somatic cytochrome *c* gene: Two classes of processed pseudogenes demarcate a period of rapid molecular evolution. Proc Natl Acad Sci USA 85:9625–9629

Groves CP (1989) A theory of human and primate evolution. Oxford University Press, Oxford

Hatefi Y (1985) The mitochondrial electron transport and oxidative phosphorylation system. Annu Rev Biochem 54:1015–1069

Irwin DM, Kocher TD, Wilson AC (1991) Evolution of the cytochrome *b* gene of mammals. J Mol Evol 32:128–144

Janke A, Feldmaier-Fuchs G, Thomas WK, von Haessler A, Pääbo A (1994) The marsupial mitochondrial genome and the evolution of placental mammals. Genetics 137:243–256

Jukes TH, Cantor CR (1969) Evolution of protein molecules. In: Munro HN (ed) Mammalian protein metabolism. Academic Press, New York, pp 21–132

Kimura M, Ohta T (1972) On the stochastic model for estimation of mutational distance between homologous proteins. J Mol Evol 2: 87–90

Lappalanien P, Watmough NJ, Greenwood C, Saraste M (1995) Electron transfer between cytochrome *c* and the isolated Cu_A domain:

Identification of substrate-binding residues in cytochrome *c* oxidase. Biochemistry 34:5824–5830

Lopez JV, Cevario S, O'Brien SJ (1996) Complete nucleotide sequences of the domestic cat (*Felis catus*) mitochondrial genome and transposed mtDNA repeat, *Numt*, in the nuclear genome. Genomics 33:229–246

Muse SV, Weir BS (1992) Testing for equality of evolutionary rates. Genetics 132:269–276

Osheroff N, Speck SH, Margoliash E, Veerman ECI, Wilms J, König BW, Muijsers AO (1983) The reaction of primate cytochrome *c* with cytochrome *c* oxidase. J Biol Chem 258:5731–5738

Sambrook J, Fritsch EF, Maniatis T (1989) Molecular cloning: A laboratory manual, 2nd ed. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY

Schmidt TR, Jaradat SA, Goodman M, Lomax MI, Grossman LI (1997) Molecular evolution of cytochrome *c* oxidase: Rate variation among subunit. VIa isoforms. Mol Biol Evol 14:595–601

Schmidt TR, Goodman M, Grossman LI (1999) Molecular evolution of the COX7A gene family in primates. Mol Biol Evol 16:619–626

Thompson JD, Higgins DG, Gibson TJ (1994) CLUSTAL W: Improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. Nucleic Acids Res 22:4673–4680

Tsukihara T, Aoyama H, Yamashita E, Tomizaki T, Yamaguchi H, Shinzawa-Itoh K, Nakashima R, Yaono R, Yosikawa S (1996) The whole structure of the 13-subunit oxidized cytochrome *c* oxidase at 2.8 Å. Science 272:1136–1144

Witt H, Malatesta F, Nicoletti F, Brunori M, Ludwig B (1998a) Cytochrome *c*-binding site on cytochrome oxidase in *Paracoccus denitrificans.* Eur J Biochem 251:367–373

Wu C-I, Li W-H (1985) Evidence for higher rates of nucleotide substitution in rodents that in man. Proc Natl Acad Sci USA 82:1741–1745

Wu W, Goodman M, Lomax MI, Grossman LI (1997) Molecular evolution of cytochrome *c* oxidase subunit IV: Evidence for positive selection in simian primates. J Mol Evol 44:477–491

Yang Z (1997) PAML: A program package for phylogenetic analysis by maximum likelihood. Comp Appl Biosci 13:555–556

Yang Z, Kumar S, Nei M (1995) A new method of inference of ancestral nucleotide and amino acid sequences. Genetics 141:1641–1650