

TABLE 4. TRIVIAL NAMES OF PURIFIED P450 PROTEINS OR DISTINCT GENE PRODUCTS WHERE A CORRELATION WITH CATALYTIC ACTIVITY HAS BEEN DEMONSTRATED

<i>Protein symbol</i>	<i>Trivial name</i>	<i>Species</i>	<i>References</i>
CYP1A1	MC-B	Rat	Guengerich (1978)
	P-448 ₂		Imai (1979)
	P-450c		Ryan <i>et al.</i> (1979)
	P-448		Masuda-Mikawa <i>et al.</i> (1979)
			Wolff <i>et al.</i> (1980)
	MC-P-448		Elshourbagy and Guzelian (1980)
	P-450MC		Harada and Omura (1981)
	P-448MC		Goldstein <i>et al.</i> (1982)
	PCB P-448-L		Kamataki <i>et al.</i> (1983a)
	MC2		Wolf and Oesch (1983)
	MC-1		Kuwahara <i>et al.</i> (1984)
	MC-I, MC-II		Sakaki <i>et al.</i> (1984)
	MC-5		Funae and Imaoka (1985)
	P-448L		Nagata <i>et al.</i> (1985)
	MC1b		Wolf (1986)
	P ₁ -450	Mouse	Negishi and Nebert (1979)
	P ₁ -450	Rabbit	Atlas <i>et al.</i> (1975)
			Atlas <i>et al.</i> (1977)
	P-450 b		Johnson and Muller-Eberhard (1977b)
	form 6		Norman <i>et al.</i> (1978)
	P-450III		Ueng and Alvares (1982)
	P-448 ₂		Aoyama <i>et al.</i> (1982)
	LM ₆		Koop and Coon (1984)
CYP1A2	P-450 HLC	Human	Shimada <i>et al.</i> (1992)
	P-450-HM-4		Ubukata <i>et al.</i> (1992)
	P-450d	Rat	Ryan <i>et al.</i> (1980)
	ISF-P-450		Fisher <i>et al.</i> (1981)
	P-448HCB		Goldstein <i>et al.</i> (1982)
	ISF-G		Guengerich <i>et al.</i> (1982)
	form 5		Lau and Strobel (1982)
	PCB P-448-H		Kamataki <i>et al.</i> (1983a)
	MC-2		Kuwahara <i>et al.</i> (1984)
	MC1		Wolf <i>et al.</i> (1984)
	P-448H		Funae and Imaoka (1985)
	MC1a		Nagata <i>et al.</i> (1985)
CYP2A1	P-448	Mouse	Wolf (1986)
	P ₃ 450		Negishi and Nebert (1979)
	LM ₄	Rabbit	Tukey and Nebert (1984)
	P-448		Haugen <i>et al.</i> (1975)
			Atlas <i>et al.</i> (1975)
			Kawalek <i>et al.</i> (1975)
			Atlas <i>et al.</i> (1977)
	P-448 ₁		Hashimoto and Imai (1976)
	P-450 c		Johnson and Muller-Eberhard (1977a)
	form 4		Norman <i>et al.</i> (1978)
CYP2B1	P-450 HD _d	Human	Wrighton <i>et al.</i> (1986a)
	P-450 _{PA}		Distlerath <i>et al.</i> (1985)
	P-450-D3	Dog	Ohta <i>et al.</i> (1989b)
	P-450-D2		Ohta <i>et al.</i> (1990)
CYP2E1	P-450a	Rat	Ryan <i>et al.</i> (1979)
	P-450 UT-F		Guengerich <i>et al.</i> (1982)
	PB-3		Waxman <i>et al.</i> (1983)
	P-452		Nagata <i>et al.</i> (1985)
	UTI		Wolf (1986)
	IF-3		Funae and Imaoka (1987)
	RLM2b		Schenkman <i>et al.</i> (1987)

TABLE 4. (CONTINUED)

<i>Protein symbol</i>	<i>Trivial name</i>	<i>Species</i>	<i>References</i>
CYP2A2	UT-4	Rat	Funae and Imaoka (1985)
	RLM2		Jansson <i>et al.</i> (1985)
	M-2		Matsumoto <i>et al.</i> (1986)
CYP2B1	P-450 PB-B	Rat	Guengerich (1978)
	P-450 ₄		Imai (1979)
	P-450b		Ryan <i>et al.</i> (1979)
	Fraction C		West <i>et al.</i> (1979)
	PB-P450		Elshourbagy and Guzelian (1980)
	P-450PB		Harada and Omura (1981)
	P-450 PB-4		Waxman <i>et al.</i> (1982)
	PB-1		Kuwahara <i>et al.</i> (1984)
	PBRLM5		Backes <i>et al.</i> (1985)
	PB-4		Funae and Imaoka (1985)
	PB _{3a}		Wolf <i>et al.</i> (1988)
CYP2B2	P-450 PB-D	Rat	Guengerich <i>et al.</i> (1982)
	P-450e		Ryan <i>et al.</i> (1982)
	P-450 PB-5		Waxman and Walsh (1982)
	PBRLM6		Backes <i>et al.</i> (1985)
	PB-5		Funae and Imaoka (1985)
	P-450 _{III}		Nagata <i>et al.</i> (1985)
	PB _{3b}		Wolf <i>et al.</i> (1988)
CYP2B4	P-450 ₁	Rabbit	Imai and Sato (1974)
	LM ₂		van der Hoeven <i>et al.</i> (1974)
	P-450 1		Avinc and Philpot (1976)
	P-450		Kamataki <i>et al.</i> (1976)
	form 2		Johnson <i>et al.</i> (1979)
CYP2B11	P-450 PBD-2	Dog	Graves <i>et al.</i> (1990)
CYP2C2	P-450 K	Rabbit	Finlayson <i>et al.</i> (1986)
	P-450 2CAA		Laethem <i>et al.</i> (1992)
CYP2C3	LM _{3b}	Rabbit	Koop and Coon (1979)
	form 3		Johnson (1980)
	P-450 _s		Aoyama <i>et al.</i> (1982)
	form 3b		Dieter and Johnson (1982)
CYP2C5	P-450 ADH	Rat	Yamada <i>et al.</i> (1989)
	form 1		Dieter <i>et al.</i> (1982)
	P-450 PB-C		Guengerich <i>et al.</i> (1982)
CYP2C6	PB-1		Waxman and Walsh (1983)
	PB _{1a} /PB _{1b}		Wolf <i>et al.</i> (1986)
	PB-2		Funae and Imaoka (1987)
	RLM5a		Schenkman <i>et al.</i> (1987)
	P-450k		Swinney <i>et al.</i> (1987)
	P-450f		Ryan <i>et al.</i> (1984b)
	RLM5b		Favreau <i>et al.</i> (1987)
CYP2C8	HLx	Human	Wrighton <i>et al.</i> (1987b)
CYP2C9	P-450 _{MP-1}	Human	Shimada <i>et al.</i> (1986)
	P-450 _{MP-2}		Shimada <i>et al.</i> (1986)
	P-450 _{meph}		Gut <i>et al.</i> (1986b)
	Human-2		Kawano <i>et al.</i> (1987)
	P-450-HM2		Komori <i>et al.</i> (1988)
	P-450 _{TB}		Srivastava <i>et al.</i> (1991)
CYP2C11	P-450 UT-A	Rat	Guengerich <i>et al.</i> (1982)
	RLM5		Cheng and Schenkman (1983a,b)
	P-450-male		Kamataki <i>et al.</i> (1983b)
	P-450 2c (PB-2c)		Waxman <i>et al.</i> (1983)
	P-450h		Ryan <i>et al.</i> (1984b)
	UT-2		Funae and Imaoka (1985)

TABLE 4. (CONTINUED)

<i>Protein symbol</i>	<i>Trivial name</i>	<i>Species</i>	<i>References</i>
CYP2C12	P-450 _{II}		Nagata <i>et al.</i> (1985)
	P-450 _{CC25}		Hayashi <i>et al.</i> (1986)
	M-1		Matsumoto <i>et al.</i> (1986)
	PB _{2a}		Wolf <i>et al.</i> (1986)
	P-450-female	Rat	Kamataki <i>et al.</i> (1983b)
	P-450i		Ryan <i>et al.</i> (1984a)
	P-450 2d		Waxman (1984)
	UT-I		Waxman <i>et al.</i> (1985)
	F-1		Matsumoto <i>et al.</i> (1986)
	F2		Funae and Imaoka (1987)
CYP2C13	fRLM4		Schenkman <i>et al.</i> (1987)
	RLM3	Rat	Cheng and Schenkman (1983a,b)
	P-450g		Ryan <i>et al.</i> (1984b)
	UT-5		Funae and Imaoka (1985)
	M-3		Matsumoto <i>et al.</i> (1986)
CYP2C14	P-450 ₄	Rabbit	Sato <i>et al.</i> (1982)
CYP2D6	P-450 _{buf}	Human	Gut <i>et al.</i> (1986)
	P-450 db1		Gonzalez <i>et al.</i> (1988b)
CYP2E1	P-450j	Rat	Ryan <i>et al.</i> (1985)
	P-450 _{ac}		Patten <i>et al.</i> (1986)
	RLM6		Favreau <i>et al.</i> (1987)
	Pyrazole P-450		Palakodety <i>et al.</i> (1988)
	P-450 LMeb	Rabbit	Ingelman-Sundberg and Hagbjork (1982)
	form 3a		Koop <i>et al.</i> (1982)
	P-450 HLj	Human	Wrighton <i>et al.</i> (1986b)
CYP2E2	P-450 _{ALC}		Lasker <i>et al.</i> (1987)
	form 3d	Rabbit	Ding <i>et al.</i> (1991a)
CYP2F2	P-450 _{Nah}	Mouse	Ritter <i>et al.</i> (1991)
CYP2G1	P450NMb	Rabbit	Ding and Coon (1988)
CYP3A1	P-450 _p	Rat	Wrighton <i>et al.</i> (1985)
	PB _{2c}		Wolf <i>et al.</i> (1986)
	PCNa		Halpert (1988)
	P-450 6β-4		Nagata <i>et al.</i> (1990a)
	P-450 PCN-E	Rat	Guengerich <i>et al.</i> (1982)
CYP3A2	P-450 PB(2a)		Waxman <i>et al.</i> (1983)
	PCNb/c		Halpert (1988)
	PB-1		Imaoka <i>et al.</i> (1988b)
	P-450 6β-1/3		Nagata <i>et al.</i> (1990)
	P-450 human-1	Human	Kawano <i>et al.</i> (1987)
CYP3A3 or 4	P-450-HM-1		Komori <i>et al.</i> (1988a)
	P-450 _{NF}		Guengerich <i>et al.</i> (1986)
	HLP3	Human	Wrighton <i>et al.</i> (1989)
CYP3A5	LM3	Rabbit	Ingelman-Sundberg and Johansson (1980)
	P-450 _{B1}		Miki <i>et al.</i> (1980)
CYP3A6	LM3c		Koop <i>et al.</i> (1981)
	P-450 _s		Aoyama <i>et al.</i> (1982)
	form 3c		Johnson <i>et al.</i> (1988)
	P-450HFLa	Human	Kitada <i>et al.</i> (1985)
CYP3A7	P-450-HM-3		Komori <i>et al.</i> (1988a)
	HLP2		Wrighton and Vandenberg (1989)
	P-450-MK2	Monkey	Ohta <i>et al.</i> (1989a)
CYP4A1	P-452	Rat	Tamburini <i>et al.</i> (1984)
	LA _ω		Hardwick <i>et al.</i> (1987)

TABLE 4. (CONTINUED)

<i>Protein symbol</i>	<i>Trivial name</i>	<i>Species</i>	<i>References</i>
CYP4A2	K-5	Rat	Imaoka and Funae (1986)
CYP4A4	P-450 PG- ω	Rabbit	Williams <i>et al.</i> (1984)
	p-2		Yamamoto <i>et al.</i> (1984)
			Kikuta <i>et al.</i> (1989)
CYP4A5	kd	Rabbit	Yoshimura <i>et al.</i> (1990)
CYP4A6	LPG ω -1		Kikuta <i>et al.</i> (1989)
	ka-1		Kusunose <i>et al.</i> (1989)
CYP4A7	ka-2	Rabbit	Kusunose <i>et al.</i> (1989)
CYP4B1	P-450 II form 5	Rabbit	Wolf <i>et al.</i> (1978) Robertson <i>et al.</i> (1983)

example, appear to have diverged more than twice as long ago as the human and chicken *CYP19* genes, yet the original *CYP17* and *CYP19* genes undoubtedly existed long before divergence of the predecessors of mammals and birds. This discrepancy points out how the topology of phylogenetic species trees (derived from fossil data) and gene trees (derived from molecular data) can differ.

Another consideration is that the *CYP17* and the *CYP19* genes are actually diverging at significantly different rates. Certain amino acids, or regions of the enzyme, might need to be retained, or conserved, for the enzyme to carry out its catalytic activity; such conservation could be a factor in nonlinearity during evolution. These conserved regions or critical amino acids probably include those docking with the NADPH-P450 oxidoreductase or cytochrome *b*₅, binding to a critical endogenous substrate, and interacting with the heme moiety.

Gene conversion events can reestablish 100% similarity in a portion (or all) of a gene that had been considerably diverged from its neighbor. There are numerous examples of gene conversion events among homologous genes in various P450 gene subfamilies, indicating that gene conversion is a major cause for "molecular drive" and the nonlinearity of P450 gene evolution (Gonzalez and Nebert, 1990). Computer programs that assume a constant rate of evolution and do not allow for gene conversion cannot be expected to make a correct tree. This is an argument against using only the unweighted-pair-group method of analysis (UPGMA), since this method assumes a constant rate of evolution and does not allow for gene conversion events. On the other hand, the neighbor-joining method does not assume constant rates of evolution (Saitou and Nei, 1987), and both methods lead to very similar P450 phylogenetic trees (Nebert and Nelson, 1991).

DIVERGENCE OF EUKARYOTES AND EUBACTERIA

Very recent geologic (Knoll, 1992) and molecular biologic (Rivera and Lake, 1992) evidence suggests that eukaryotes and eocyte prokaryotes are immediate relatives (Fig. 1). Such an emerging concept is very exciting, because it would suggest that any gene occurring in both eubacteria

and eukaryotes probably arose from a common ancestral gene more than 3.5 billion years ago (Loomis, 1988). Each P450 enzyme that has been studied—without exception—has been found to metabolize endogenous substrates and/or substrates used as an energy source. Therefore, it seems very likely that P450 enzymes originated during early evolution, shortly after the appearance of superoxide dismutase, to provide the organism with oxidative and peroxidative metabolism of important endogenous molecules, as well as the breakdown of environmental chemicals utilized for energy. Subsequently, the P450 enzymes in eukaryotes probably diversified more recently, in response to the adverse effects of dietary pressures and other environmental chemicals (Gonzalez and Nebert, 1990).

NITRIC OXIDE SYNTHASES: AN EXAMPLE OF CONVERGENT EVOLUTION?

The nitric oxide (NO) synthases form diatomic NO, which appears to play an important role in neurotransmission and muscle contractility (Nathan and Hibbs, 1991; Lowenstein and Snyder, 1992). The NO synthases contain a carboxy-terminal domain with sequence similarity to NADPH-P450 oxidoreductase (Bredt *et al.*, 1991). Recently, evidence has been presented for heme and biochemical features indicative of a P450-like function (White and Marletta, 1992), presumably in the amino-terminal half of the NO synthase molecule. It is well known that P450 proteins have the signature sequence FXXGXXXCXG, present in 202 of 205 sequences; each of the three exceptions only involves one of the three established noncysteine residues. This signature sequence is not present in the NO synthases. There are seven conserved cysteines in the amino-terminal region of NO synthase before the calmodulin-binding domain. Two of these fit the CXG pattern at nucleotides 101 and 186 of the bovine sequence (Lamas *et al.*, 1992). The first is not a conserved region. The second is in a highly conserved region and is the best candidate for a heme-thiolate ligand—based on sequence similarity, but not based on location in the protein sequence.

To search for resemblance to P450 sequences, we aligned the mouse NO synthase amino-terminal 501 amino acids with 57 P450 sequences, each from a different sub-

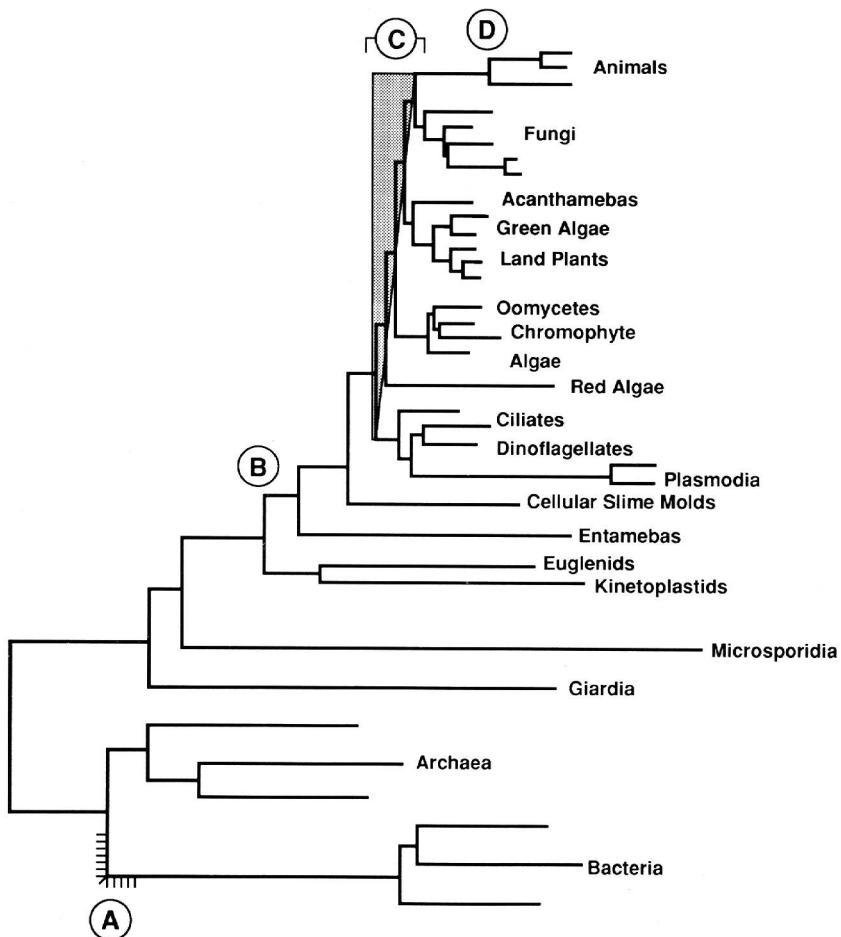


FIG. 1. Molecular phylogeny of eukaryotic organisms based on sequence comparisons of small-subunit rRNA and constructed by distance matrix methods. The *hachured lines* denote the position of the tree root, as inferred from analysis of protein sequences. A. The diversification point of the major domains, 3.5 billion years ago or earlier. B. The acquisition of mitochondria, inferred from the geochemical record to be between 2.8 and 2.4 billion years ago. C. The major radiation of phenotypic diversity of eukaryotes, suggested on the basis of fossils to be 1.5–1.0 billion years ago. D. The radiation of coelomate animal phyla, about 560–540 million years ago. (Reproduced, with permission, from Knoll, 1992.)

family, using ALIGN from the FASTA package. The percent identity ranged from 8.9 to 15.6, with an average of 11.6%, about what would be expected for random amino acid sequences. In P450 proteins, the thiolate cysteine is near the carboxyl end of the molecule. If the Cys-186 is the thiolate of NO synthase, this cysteine is very close to the amino-terminus and all of the structural features needed for a P450 enzyme could not be encoded by only 186 amino acids. If the last conserved cysteine (Cys-433 for bovine NO synthase) is the thiolate ligand, a conventional structure could be produced around residue 433—with the pattern of EXXA/CXXXCXA. A search for other conserved segments found in P450 sequences failed to identify anything in the NO synthases. The “I helix” (Poulos *et al.*,

1987) conserved sequence was not found. Neither the PYTDA-like sequence nor the PERF/W sequence was found.

Because all P450 sequences from bacteria to mammals have a strict motif that is absent in all NO synthases, our conclusion is that divergence from a P450 sequence is highly unlikely. The sequence identity was found to be approximately random for 57 P450 sequences, and key conserved regions in P450 sequences are absent in NO synthases. It is conceivable that the Cys-433 is the thiolate ligand and that this sequence has diverged very long ago—prior to the divergence of eubacteria from eukaryotes—so that we no longer recognize the Cys-433 region as a P450 signature sequence. Alternatively, it is possible that

Cys-186 is the thiolate ligand and that the function of NO synthase as a P450-like enzyme represents an example of convergent evolution.

Although convergent evolution is more likely, crystalline structure studies of NO synthase could prove this possibility to be incorrect. For example, heat shock protein 70 (HSP70), prokaryotic cell cycle proteins, sugar kinases, and actin all have no recognizable sequence similarity, yet their ATPase domains have probably descended from a common ancestor based on their crystal structures (Bork *et al.*, 1992). The only question, then, is why do the other P450 sequences retain their signature motifs, even after more than 3.5 billion years? Therefore, we believe that these motifs are essential to the P450 gene superfamily and that the NO synthases are unique and an example of convergent evolution.

CLOSING REMARKS

We urge everyone to request free advice from the co-authors of this update about assignments for newly determined P450 sequences, so that manuscripts being written will contain the least amount of ambiguity. There have been several instances in the past where this was not done, and the subsequent publication has caused unnecessary confusion. All unpublished sequences have been, and will continue to be, held in the strictest confidence.

These nomenclature updates have occurred regularly at 2-year intervals since 1987, and, until this update, the total number of P450 genes in each review has more than doubled. In this 2-year period, we have seen a decreasing number of newly sequenced human/rat/mouse/rabbit/cow genes and an increasing number of other mammalian, as well as nonvertebrate and bacterial, P450 gene sequences. This might reflect: (i) more laboratories studying regulation of the genes already cloned; (ii) difficulty in cloning cDNAs from very low-abundance and noninducible mRNAs, as well as cell type-specific P450 gene expression; (iii) heightened interest among laboratories studying these genes in nonvertebrate animals, plants, and bacteria; or (iv) some combination of these factors. Because of the slow-down in newly discovered P450 genes, however, it is possible that the next nomenclature update will be published at some time longer than the 2-year intervals that have occurred in the past.

We hope that this unified nomenclature will continue to be useful to the P450 field in general and adopted by all our colleagues. The nomenclature system described herein shall be used in all publications by the authors of this report.

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