This Week's Citation Classic

Nebert D W, Adesnik M, Coon M J, Estabrook R W, Gonzalez F J, Guengerich F P, Gunsaius I C, Johnson E F, Kemper B, Levin W, Phillips I R, Sato R & Waterman M R. The P450 gene superfamily: recommended nomenclature. *DNA* 6:1-11, 1987. [Lab. Develop. Pharmacol.. Natl. Inst. Child Health & Hum. Develop., and Lab. Mol. Carcinogen., Natl. Cancer Inst., NIH. Bethesda, MD; Dept. Cell Biol., NYU Sch. Med., NY; Dept. Biol. Chem.. Univ. Mich., Ann Arbor. MI; Dept. Biochem.. Univ. Texas Hlth. Sci. Ctr., Dallas, TX; Dept. Biochem. and Or. Mol. ToxicoL Vanderbilt Univ. Sch. Med., Nashville, TN; Dept. Biochem. and Dept. Physiol. and Biophys., Univ. Illinois. Urbana, IL; Dept. Basic and Clin. Res., Scripps Clin. & Res. Fdn.. La Jolla. CA; Lab. Exp. Carcinogen. and Metab.. Roche Inst. Mol. Biol., Nutley, NJ; Dept. Biochem., St. Bartholomew's Hosp. Med. Coll., Univ. London, England; and Inst. Protein Res., Osaka Univ., Japan]

This paper is the first of a series of nomenclature updates on the P450 gene superfamily, which have appeared as page 1 in the January issue of the same journal every other year. The nomenclature system, based on divergent evolution, has been widely accepted and is used almost uniformly throughout the world today. This evolutionary analysis has fostered an appreciation for the ubiquitous distribution of P450 genes amongst eukaryotes and prokaryotes and the diversity of P450 functions ranging from drug metabolism to signal transduction. [The *SCI* ® indicates that this paper has been cited in more than 580 publications.]

Naming Related P450 Genes, Based on Divergent Evolution

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In the 1960s, 1970s, and early 1980s, it was common practice to characterize and correlate a cytochrome P450 enzyme activity with a partially purified protein (antigen) and/or antibody. Each laboratory then assigned the P450 its own name, few investigators were willing to share antigens or antibodies, and it seemed increasingly likely that the same mammalian P450 was being given three or more names. During the 1970s and early 1980s, there had been committee meetings to wrestle with the idea of a common P450 nomenclature, but no laboratory wished to discard its own favorite names. There was also a general consensus that the total number of P450 enzymes was "no more than half a dozen," or maximally 10 to 20. Almost everyone laughed when I suggested[1] that the number of P450 genes might range into the hundreds or thousands.

In the early 1980s, the National Institute of Child Health and Human Development's Laboratory of Developmental Pharmacology and other labs began to clone and sequence P450 cDNAs, leading to deduced amino acid sequences whose alignments could be compared. By spring of 1985 we had access to more than a dozen sequences in the superfamily, and it became clear to me that bacterial and mammalian P450 genes had arisen from a common ancestral gene. Using divergent evolution also seemed to me to be the easiest method for naming P450 genes, and the best solution for agreement on a common nomenclature system (which favored no laboratory's pet names). In early 19851 asked Lee Hood (Caltech) how the immunologists came to agree upon the nomenclature of genes in the complicated immunoglob-ulin superfamily, and he suggested that I "convene a small group of colleagues in the field and just do it." This process was begun at the Airlie House (April 1985, Airlie, Virginia), and the first members of this nomenclature committee became coauthors of this *Citation Classic* ®. Following letters and discussions with numerous evolutionary biologists, I proposed criteria for the assignment of newly discovered P450 genes to new or existing families or subfamilies; these criteria were rigorously argued, expanded, and agreed upon by our P450 nomenclature committee during the next 18 months.

This process has been successfully repeated and improved at two-year in-

tervals,[2-4] with new interested colleagues being invited to replace previous coauthors. From less than 50 genes in the 1987 update, this number has presently increased to 221 genes and 12 putative pseudogenes in 31 eukaryotes (including 11 mammalian and 3 plant species) and 11 prokaryotes. It is now likely that any mammalian species has at least 60, and perhaps more than 200, distinct cytochrome P450 (CYP) genes, almost all of which encode a unique enzyme.[4]

Why should there be so many CYP genes? One likely explanation—at least in animals during the last 400 million years—is the evolving of new genes by molecularly driven duplication events, in response to dietary pressures surrounding animal-plant interactions;[5] the same is expected, of course, to be found in plants. It is now clear, however, that the ancestral CVPgene probably arose more than 3.5 billion years ago.[4] What could the CYP genes, and other so-called "drug-metabolizing enzyme" genes, be doing way back then? The up-regulation (induction) of many CYP genes is known to be caused by exposure to innumerable foreign chemicals, drugs, and environmental pollutants, and changes in the levels of endogenous hormones and peptide signals. Recently, however, colleagues in a vast range of disciplines have been stumbling across CYP genes, expressed during such diverse processes as: contractility of the ductus venosus and ductus arteriosis in mammalian heart; spontaneous hypertension and ion transport in the renal medulla; differentiation; participation by the arachidonic acid and cytokine cascades; insect-plant synergism; neuropeptide GTP-mediated regulation of heme synthesis in the cockroach; gonadotropic hormone regulation in the pond snail; sporulation in yeast; cell division; the ripening and wounding of plants and the virulence of viral and bacterial pathogens in plants; responses to nitrate and nitrite concentrations in fungus, and nitrogen fixation in bacteria.The involvement of CYP genes in such diverse regulatory processes suggests a critical role of these genes—controlling the steady-state levels of ligands involved in ligand-modulated transcription[6]—in signal transduction pathways that effect growth, cell division, morphogenesis and mating, homeostasis, proliferation, and neuroendocrine functions.

Why is the 1987 paper a Citation Classic®? A decade ago, the "cytochrome P450 crowd" concentrated almost exclusively on redox enzymology and biochemistry, hemoprotein biophysics, and studies of steroidogenesis, drug metabolism, and metabolic activation of environmental promutagens and procarcinogens. Now—for these scientists, but especially for scientists outside the traditional P450 field—this nomenclature system provides a simplified basis for understanding the evolution and function of these novel and ubiquitous genes in this very ancient superfamily. It seems likely that the more recent nomenclature updates will also become Citation Classics.

1. **Nebert D W.** Multiple forms of inducible drug-metaboiizing enzymes: a reasonable mechanism by which any organism can cope with adversity. *Mot. Cell. Biochem.* 27-27-46, 1979. (Cited 145 times.)
2. **Nebert D W, Nelson D R, Adesnik M, Coon M J, Estabrook R W, Gonzalez F J, Guengerich F P, Gunsalus I C, Johnson E F, Kemper B, Levin W, Phillips I R, Sato R & Waterman M R.** The P4S0 gene superfamily: update on the naming of new genes and nomenclature of chromosomal loci. *DNA* 8:1-13, 1989. (Cited 550 times.)
3. **Nebert D W, Nelson D R, Coon M J, Estabrook R W, Feyereisen R, Fujii-Kuriyama Y, Gonzalez F J, Guengerich F P, Gunsalus I C, Johnson E F, Loper J C, Sato R, Waterman M R & Waxman D J.** The P450 superfamily: update on new sequences, gene mapping, and recommended nomenclature. *DNA Cell Biol.* 10:1-14, 1991. (Cited 440 times.)
4. **Nelson D R, Kamataki T, Waxman D J, Guengerich F P. Estabrook R W, Feyereisen R, Gonzalez F J, Coon M J. Gunsalus I C, Gotoh O, Okuda K & Nebert D W.** The P450 superfamily: update on new sequences, gene mapping, accession numbers, early trivial names, and nomenclature. *DNA Cell Biol.* 12:1-51. 1993.
5. **Gonzalez F J & Nebert D W.** Evolution of the P450 gene superfamily: animal-plant "warfare," molecular drive, and human genetic differences in drug oxidation. *Trench Genet.* 6:182-6, 1990.
6. **Nebert D W.** Proposed role of drug-metabolizing enzymes: regulation of steady-state levels of the ligands that effect growth, homeostasis, differentiation, and neuroendocrine functions. *Mol. Endocrinol.* 5:1203-14, 1991.