Clinical importance of the cytochromes P450

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The human cytochrome P450 (CYP) superfamily comprises 57 genes. These genes code for enzymes that can have a role in: metabolism of drugs, foreign chemicals, arachidonic acid and eicosanoids; cholesterol metabolism and bile-acid biosynthesis; steroid synthesis and metabolism; vitamin D, syntheses and metabolism; retinoid acid hydroxilation; and those of still unknown function. Cytochrome P450 was once believed to be mainly a hepatic drug detoxification system, but is now understood to include a myriad of enzyme reactions implicated in important life processes. Mutations in many CYP genes cause inborn errors of metabolism and contribute to many clinically relevant diseases.

Cytochrome P450, a cellular chromophore, was first named in 1961, because the pigment (P) has a 450-nm spectral peak when reduced and bound to carbon monoxide. P450 was thought to be one enzyme in the early 1960s, and by the mid 1960s it was associated with drug and steroid metabolism. By the late 1970s, as many as six P450 enzymes were speculated to exist; however, the membrane-associated and hydrophobic nature of the enzyme system impeded purification, and the number of proteins involved could not be accurately counted. Advances in mRNA purification in the early 1980s allowed Gonzalez and colleagues1 to isolate the first cDNA encoding a complete cytochrome P450 (CYP) protein, and thereafter, results of many cloning studies have revealed dozens of different enzymes. Sequence comparisons indicated extensive similarity between cytochromes P400 identified in man and bacteria, and suggested that the superfamily originated from a common ancestral gene some three billion years ago.2 A systematic nomenclature scheme for the CYP gene superfamily, based on divergent evolution, has been in place for 15 years, and continues to be developed on the internet.3,4

Cytochrome P450 proteins are conveniently arranged into families and subfamilies on the basis of percentage homology within sequence identity.5,6 Enzymes that share >50% identity are assigned to a particular family designated by an Arabic numeral, whereas those sharing >35% identity make up a particular subfamily designated by a letter. For example, the steroid 27-hydroxylase enzyme and the vitamin D, 24-hydroxylase enzyme are both assigned to the CYP27 family because they share >30% sequence identity. Sterol 27-hydroxylase is further assigned to the CYP27A subfamily, and vitamin D, 24-hydroxylase assigned to CYP27B, because their protein sequences are <35% identical. If an additional enzyme were to be discovered that shared >50% identity with the sterol 27-hydroxylase, then it would be named CYP27A2, etc. Development and application of this beautifully logical system of nomenclature has eliminated the confusion that frequently plagued naming of other gene families and superfamilies.

Presently, there are more than 270 different CYP gene families, with 18 recorded in mammals.4 Because diversity of small molecules in plants is enormous, these organisms were predicted to contain many cytochrome P450 enzymes.3 This expectation was met in the genome of the tiny mustard plant Arabidopsis thaliana, which contains 249 active CYP genes and 24 non-functional pseudogenes, a remarkable 1% of its total gene number. The genome of the rice plant is similar, with at least 324 functional genes reported up to now.4 By contrast, human beings have 57 CYP genes and 33 pseudogenes arranged into 18 families and 42 subfamilies (panel 1), and this number is not likely to change—unless active members of the human CYP2G and CYP2T subfamilies are found.1 Advances in molecular biology and genomics facilitated the biochemical characterisation of individual P450 enzymes, which in turn revealed many surprises about an enzyme system once believed to metabolise drugs mainly in the liver. First, the cytochromes P450 act on many endogenous substrates, introducing oxidative, peroxidonic, and reductive changes into small molecules of widely different chemical structures. Substrates identified to date include saturated and unsaturated fatty acids, eicosanoids, steroids and steroids, bile acids, vitamin D, derivaties, retinoids, and uroporphyrinogens. Second, many cytochrome P450 enzymes can metabolise various exogenous compounds including drugs, environmental chemicals and pollutants, and natural plant products.6,7 Third, metabolism of foreign chemicals frequently results in metabolites that are toxic or tumorigenic, and are capable of inducing or eliciting immune responses. Forth, expression of many P450 enzymes is often induced by accumulation of a substrate.6 For example, hepatic concentrations

Search strategy and selection criteria

Medical and PubMed databases from 1966 until April 2002, were searched for P450 reviews and primary articles related to the CYP genes, CYP enzyme metabolism of both endogenous and exogenous substrates, and relevance to clinical disease. Specific keywords we used included cytochrome P450, monooxygenase, and drugs, xenobiotics, environmental chemicals, and natural products. The searches resulted in 1972 relevant citations, which were reviewed individually, to select and report the 210 most relevant documents. Citations were ordered on the basis of relevance to the topics covered, without any bias toward author or journal.
of the human CYP3A enzymes are increased by consumption of drugs such as rifampicin, which are prescribed for bacterial infection. This induction not only increases rifampicin metabolism but also leads to enhanced clearance of other drugs that are CYP3A substrates. Because rifampicin also induces several CYP2C enzymes, this process would lead to more rapid clearance of CYP2C substrates. The ability of one P450 substrate to affect the concentrations of another in this manner is the basis for so-called drug-drug interactions, which complicate treatment.

Availability of cloned genes, and the biochemical and immunochemical probes derived from these cDNAs, has given us new insight into the diverse biological and clinical roles of individual cytochromes P450. Their biological functions include metabolism of endogenous substrates and synthesis of endogenous hydrophobic lipids such as cholesterol, bile acids, steroid hormones, and fatty acids. Below, we summarise the physiological roles of the various human cytochromes P450 and how these enzymes affect clinical outcomes.

**Metabolism of foreign chemicals, arachidonic acid, and docosahexaenoic acid**

**Foreign chemicals**

Foreign chemicals (sometimes called xenobiotics) include drugs, plant-derived or fungal-derived secondary metabolites consumed with food, and thousands of environmental pollutants—eg, halogenated hydrocarbons, polycyclic aromatic hydrocarbons, amines, ingredients of combustion, industrial complex mixtures, herbicides, pesticides, etc. Human cytochromes P450 that metabolise these foreign chemicals are almost exclusively in the CYP1, CYP2, CYP3, and to a lesser degree, CYP4 families. Many allelic variants exist within each of these gene families, resulting in pharmacogenetic heterogeneity between individuals.

A database of human allelic variants of CYP genes is maintained on the Internet, which uses a consistent classification system. In brief, the consensus, or reference, sequence (\*1 allele) generally encodes an efficient-metabolism phenotype, whereas variant alleles encode a poor-metabolism phenotype, with low or no enzyme activity towards a particular drug. On occasion, because of one or more gene duplications, a variant genotype might indicate a very high ultra-metabolism phenotype. Different alleles of the CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP2A6, and CYP2B6 drug-metabolising genes can thus result in treatment failure, toxic effects, and even death in rare cases. Simultaneously, rates of detoxication, and sometimes of metabolic activation, of environmental chemicals can be strikingly different between individuals with different CYP haplotypes. Examples of metabolic activation can be seen in the CYP2D6, CYP2C19, CYP3A4, and CYP2B6 genes. Although data are very convincing in animals, confirmation of such associations in clinical populations remains difficult.

**CYP1 gene family**—Expression of the CYP1 genes is induced by aryl hydrocarbon receptors, a transcription factor that is activated by binding of polycyclic aromatic hydrocarbons, such as those found in industrial incineration products, cigarette smoke, and charred-grilled food. CYP1A1 and CYP1B1 are expressed in varying amounts in different tissues, and are most efficient metabolising polycyclic aromatic hydrocarbons, whereas CYP1A2 preferentially metabolises arylamines and N-heterocycles. CYP1A1, and possibly CYP1A2 and CYP1B1, metabolise an as-yet-to-be-identified endogenous ligand for the aryl hydrocarbon receptor, and CYP1A2 also inactivates prostaglandin \( \Delta^3 \) and \( \Delta^4 \). CYP1A2 and CYP1B1 hydroxylate steroids at the carbon-2 and carbon-4 positions, respectively, and CYP1A2 oxidises urea in oxidase. On the other hand, CYP1A2 metabolises about 10-20 different drugs, whereas CYP1A1 and CYP1B1 do not seem to act mainly on drugs. Reasons for the unusually high expression of CYP1A1 in some types of solid tumours are not known, but this occurrence might be useful in designing drugs for chemotherapeutic intervention. All three CYP1 enzymes detoxify or activate many environmental carcinogens.

Although many alterations in carboxylic acid and drug metabolism are recorded in mice without the Cyp1a1, Cyp1a2, and Cyp1b1 genes, such animals are viable, suggesting that the encoded P450 enzymes are either redundant or do not have an essential role in metabolism of endogenous compounds. On the other hand, mutations in the human CYP1B1 gene cause primary congenital glaucoma (buphthalmos) (panel 2); this clinical observation suggests that development of the anterior chamber of the eye during embryogenesis requires metabolism of an important endogenous substrate by CYP1B1. Since CYP1B1 seems to have a role in retinoid acid biosynthesis and degradation, this fact might help to explain the cause of primary congenital glaucoma. However, in view of their overlapping substrate specificities, if CYP1B1 has a role in the retinoid acid
pathway, what about CYP1A1 and CYP1A2? Possibly related to this discussion, mice with a disruption in the Atr gene accumulate liver retinoids, and metabolism of retinoid acid is reduced.8

CYP2 gene family—CYP2 is the largest P450 family in mammals (panel 1). Human CYP2C, CYP2C9, CYP2C18, and CYP2C19 together metabolise to varying amounts—greater than half of all frequently prescribed drugs, and arachidonic acid and some sterols. Results of in-vitro biochemical assays show that CYP2D6 metabolises more than 75 drugs.9 CYP2A6, CYP2A13, CYP2B6, CYP2B1, CYP2E1, and CYP2J3 also help to metabolise some drugs.10 Functions of other members of this family—including CYP2A2, CYP2R1, CYP2S1, CYP2U1, and CYP2W1—are presently unknown. Although enzymes of the CYP2C subfamily are generally thought to have a role in drug metabolism, a β-lactamase-like function is suggested by the similarity of the CYP2C2 enzyme to that found in the β-lactamase of the antibiotic.11 This association explains a recent finding in P340 published work.11, 12 Most CYP gene products in vertebrates probably first evolved for important functions, before then developing para-metabolite-degradation and drug-metabolism abilities. Although the CYP2C and CYP2D subfamilies encode functional genes in rodents, they only seem to encode pseudogenes in man, suggesting that whatever functions these genes had about 80 million years ago (at the time of the mammalian radiation), they are no longer needed in man. Mice deficient in the Cyp2e1 gene seem to be outwardly normal, but are very resistant to benzene toxic effects,17 indicating a role in xenobiotic metabolism for this subfamily.

CYP3 gene family—The CYP3 family has four members (panel 1). CYP3A4 and CYP3A5 are the most abundantly expressed P450 enzymes in the human liver and gastrointestinal tract, and are known to metabolise more than 120 frequently prescribed drugs,16 and endogenous substrates such as steroids and bile acids.16 Of particular clinical importance, metabolism of certain antifungal and immunosuppressive drugs by CYP3A4 and CYP3A5 could lead to insufficient amounts of these drugs in extensive-metaboliser patients, and excessive concentrations in those with the poor-metabolism phenotype, when either type of patient is given the same dose of the drug.16 The function of hepatic CYP3A43 is not yet known. CYP3A7 is expressed in fetal liver, and the uridine endometrium, but its role in these tissues is not known.

In the CYP3A subfamily, an important regulatory pathway controlling expression in the liver and gut has been reported.17 Evidence suggests that drugs of diverse structure can induce members of this family, and that the capacity of a particular compound to induce CYP3A enzymes varies between species.18 The molecular basis of induction was traced to a ligand-activated transcription factor, which is known as the pregnane X receptor (PXR), pregnane-activated receptor, or steroid and xenobiotic receptor. This protein is a member of the nuclear hormone receptor superfamily, which binds small molecules and activates transcription of CYP3A genes containing a particular DNA motif or response element sequence in their regulatory regions. Interspecies differences in induction of CYP3A enzymes by a particular drug show ability of the compound to interact with the ligand-binding domain of the PXR receptor.6

Evidence of this regulatory system and its pharmological properties explains the long mysterious ability of certain drugs to protect an organism from the toxic effects of other compounds.19 For example, derivatives of the steroid pregnenolone can attenuate the hepatocytotoxicity associated with ingestion of indomethacin and digitoxin. Pregnenolone-related compounds are ligands for the PXR and induce synthesis of CYP3A subfamily members, which in turn inactivate the offending substance. The function of hepatic hypericum, the active agent in St John’s wort, a herbal remedy widely used for treatment of depression. Hypericum activates the PXR and CYP3A genes, leading to enhanced metabolism of many compounds—including prescription drugs—and their attendant adverse clinical events.4, 20 Our future ability to predict drug-drug interactions and to design new treatments should be greatly aided by screens using the PXR and its CYP3A target genes.

Some CYP2B and CYP2E1 genes are induced by phenobarbital and other drugs by another member of the nuclear hormone receptor superfamily—the constitutive androstane receptor (CAR)—and by PXR. Although CAR and PXR response elements or DNA motifs in the regulatory regions of these genes are distinct—it has now been established that CAR can activate CYP2E1 genes via PXR response elements and that PXR can regulate CYP2B1 genes via the CAR or phenobarbital response element.21 This cross-talk between receptor transcription factors suggests an extra layer of protection against the harmful effects of toxic compounds such as plant.
metabolites or drugs but, at the same time, increases the propensity for drug-drug interactions.

**CYP4 gene family**—The CYP4 family has 12 members (panel 1). CYP4A11, CYP4A15, CYP4F2, and CYP4F5 metabolise some drugs but mainly have a role in metabolism of fatty acids, arachidonic acid, leukotrienes, prostaglandins, epoxyeicosatrienoic acids, (EETs) hydroxyeicosatrienoic acids (HETEs), and hydroperoxyeicosatetraenoic acids (HPETEs). CYP4F8, CYP4F11, CYP4F12, and CYP4F22 seem to be implicated in arachidonic acid and fatty-acid metabolism. Functions of CYP4A10, CYP4A22, CYP4V4, and CYP4X1 are unknown. Peroxisome proliferator-activated receptors (PPARs, γ1, γ2, and 6 classes), which are also members of the nuclear receptor superfamily, play a part in regulation of CYP4A and CYP4B genes. Several CYP4A and CYP4B enzymes are expressed in the distal convoluted tubules of the kidney, and defects in some CYP4 genes cause alterations in salt metabolism, water balance, and arterial blood pressure (panel 2). Most studies of blood pressure have been done in rats, although human kidney CYP4A11 and CYP4F2 have also been shown to convert arachidonic acid to 20-HETE.

**Arachidonic acid and eicosanoids**

All cytochrome P450 enzymes probably have one or more endogenous functions, in addition to metabolism of foreign chemicals and plant compounds from which all drugs are derived. Examples of this dual function are seen in the cytochrome P450 enzymes that metabolise arachidonic acid, which is converted into more than 100 eicosanoids metabolites (figure 1). Up to now, 14 cytochrome P450 enzymes in the CYP1, CYP2, CYP3, and CYP4 families have been shown to participate in epoxygenation, reduction, and oxidation of these second-messenger molecules. Prostaglandins D2, E6, E3, and EETs, HETEs, and HPETEs have a role in many life processes, including: renal vasomotor control; bronchodilation; bradycardia; oedema; intestinal vasodilation; smooth-muscle contraction; allergic response; mitogenesis; chemotaxis; inhibition of platelet aggregation and de-sensitisation; bone resorption; fever generation; modulation of ion transport; enhanced peptide secretion; mobilisation of intracellular calcium; modulation of the sodium and potassium ATPase; egg formation; and pain response. Diseases caused by mutations in P450 enzymes that participate in metabolism of arachidonic acid have yet to be described, but almost certainly exist.

The thromboxane A2 synthase (CYP41A) and prostacyclin synthase (CYP41A) genes encode P450 enzymes with opposite roles in blood clotting. Thromboxane A2, the product of the CYP41A enzyme, is a fatty-acid metabolite that decreases cyclic AMP levels in platelets and, in so doing, stimulates their ability to aggregate. By contrast, CYP4A1 forms prostacyclin (also called prostacyclin), which raises intracellular cyclic AMP concentrations and inhibits platelet aggregation. Mutations in the CYP41A or CYP41A genes are thus predicted to lead to clotting and inflammatory disorders, including coronary artery disease and pulmonary hypertension.

**Cholesterol metabolism and bile-acid biosynthesis**

At least seven, possibly nine, cytochrome P450 enzymes have a role in conversion of acetoacetic sterols and bile acids (figure 2). Lanosterol 14α-desmolase, which is encoded by the CYP41A1 gene, is pivotal in the synthesis of cholesterol, removing two methyl groups via oxidative reactions from the intermediate lanosterol. The CYP41A1 enzyme is the target of antifungal drugs such as ketoconazole, and is one of the most evolutionarily conserved of all cytochromes P450. Genes encoding this enzyme are found in plants, fungi, animals, and even in the primitive prokaryote *Mycobacterium* subspecies. The CYP41 gene seems to have been lost in other phylogenetic branches, such as the nematode *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster*, and the sea squirt *Ciona savignyi*. The widespread distribution of this enzyme across phyla and kingdoms has led to speculation that it might represent an ancestor to all eukaryotic cytochromes.

Syntesynthesis of bile acids from cholesterol represents the major catabolic route for removal of cholesterol in mammals. Hydroxylation of the ring structures in cholesterol, plus oxidation and shortening of the eight-carbon side-chain, produces water-soluble bile acids with powerful detergent properties. These metabolic transformations are catalysed in part by at least seven different P450 enzymes, including members of the CYP1, CYP2, CYP3, and CYP4 families (figure 2). CYP7A1, CYP7B1, and CYP7A1 initiate the synthesis of bile acids from cholesterol and oxysterol substrates by introduction of a hydroxyl group in the α-configuration at carbon-7 of the B-ring. The farnesoid-X receptor (also called the bile acid receptor), which is a member of the nuclear hormone receptor superfamily, is implicated in regulation of the CYP7A1 gene; mice without the Fxr gene have increased concentrations of bile acids, cholesterol, and triglycerides, and proatherogenic serum lipoprotein. CYP7B1 is a sterol 12α-hydroxylase that is essential for synthesis of the primary bile acid, cholate. CYP27A1 is a sterol 27α-hydroxylase with a role in synthesis of oxysterols and oxidation of the sterol side-chain. CYP46A1 also catalyses formation of oxysterols.
Steroid synthesis and metabolism

Six cytochrome P450 enzymes participate in steroidogenesis (figure 3). During sexual differentiation of the genital ridge in early embryogenesis, the transcription factor steroid-factor-1, a member of the nuclear hormone receptor gene family, is pivotal in upregulation of P450 genes implicated in steroid hormone synthesis—including members of the CYP11, CYP17, CYP19, and CYP21 families. CYP11A1, CYP11B1, and CYP11B2 are mitochondrial enzymes. CYP17A1 is needed for synthesis of cortisol and testosterone and oestrogen, whereas CYP19A1 converts androgenic precursors into oestrogens. Both CYP17A1 and CYP19A1 are located within the endoplasmic reticulum.

CYP17A1 is a dual-function enzyme, catalysing 17α-hydroxylation of steroid substrates and cleavage and oxidation of their side-chains. Mutations in CYP17A1 that impair both these enzymatic activities lead to deficiencies in production of glucocorticoids and sex steroids, whereas those that prevent oxidation and shortening of the side-chain lead to deficiencies in sex steroids only (panel 2). Mutations in CYP11A1 are the cause of lipid adrenal hyperplasia, whereas defects in CYP11B1 produce 11β-hydroxylase deficiency. Allele-specific mutations in CYP11B2 cause either corticosterone methyl oxidase type I deficiency or corticosterone methyl oxidase type II deficiency, and recombination events between the two closely-linked CYP11B1 and CYP11B2 genes on chromosome 8 that encode functional chimeric enzymes cause glucocorticoid-remediable aldosteronism (panel 2).

CYP19A1 synthesizes oestrogen by aromatisation of the A ring of the androgenic steroid substrates. Loss-of-function mutations in CYP19A1 cause androgen excess, which leads to improper virilisation in males and hypervirilisation in females; affected males and females also have skeletal abnormalities, indicating the essential role of oestrogens in bone formation. Rare gain-of-function mutations in CYP19A1 produce gynecomastia in males.
Hydroxylation of steroid precursors at carbon-21 is an essential step in biosynthesis of glucocorticoids and mineralocorticoids, and is catalyzed by CYP21A2 (figure 3). Mutations that disrupt 21-hydroxylation underlie more than 90% of cases of congenital adrenal hyperplasia, an exceptionally prevalent genetic disease. Three categories of this disorder are known, including salt-wasting with masculinization of females and life-threatening low sodium, high potassium, and hypervolaemia (classic); simple virilising congenital adrenal hyperplasia; and minor impairment of CYP21 activity (non-classic). Congenital adrenal hyperplasia can also be caused by mutations in the CYP21A2, CYP11B1, CYP11B2, CYP17A1, or CYP17A1 genes (panel 2).

Vitamin D synthesis and metabolism

Four P450 enzymes, including three located in mitochondria and one in the endoplasmic reticulum, participate in synthesis and breakdown of 1α,25-dihydroxyvitamin D₃, the ligand of the vitamin D₃ receptor, which is a member of the nuclear hormone receptor superfamily. This receptor-ligand system is responsible for modulation of the export of calcium from bone and absorption of calcium from the gastrointestinal tract (figure 4). CYP27A1 and porcine CYP2D25 are mitochondrial and microsomal enzymes, respectively, that form 25-hydroxyvitamin D₃ from the vitamin D₃ precursor, cholesterol.⁹ Both enzymes are abundantly expressed in the liver, in which CYP27A1 also has a major role in synthesis of bile acids (see above). In the pig, CYP2D25 seems to be the more important of the two 25-hydroxylating enzymes. Mutations in human beings that eliminate CYP27A1 activity cause a bile-acid-deficiency phenotype (cholestrointestinal xanthomatosis) but have little or no effect on vitamin D₃ metabolism.⁹

Five CYP2D genes have been reported in the mouse and in the rat, an unknown number in the pig, but only one (CYP2D6) in man.⁶ Because the CYP2D subfamily has existed for more than 450 million years, it seems highly probable that human CYP2D6 has retained the steroid 25-hydroxylation function similar to that of the pig CYP2D25 enzyme. A nucleolar receptor transcription factor, hepatic nuclear factor-4α (HNF-4α), controls expression of the human CYP2D6 gene; curiously, an 18-fold rise in serum bile acids was reported in mice without the Hnf-4α gene, which is associated with loss of CYP2D6 enzyme activity.⁷ Perhaps this effect might be explainable by a yin-yang relation between the CYP27A1 and CYP2D6 enzymes; loss of CYP2D6 expression might upset the balance and lead to CYP27A1 overexpression with resultant increases in bile acid production (figure 2), whereas loss of CYP27A1 activity causes bile acid deficiency,⁶ as mentioned above. A study of bile-acid metabolites and 25-hydroxyvitamin D₃ concentrations would be informative, comparing patients with the CYP2D6 efficient-metabolism, poor-metabolism, and ultra-metabolism phenotypes, to establish if alterations in the CYP2D6 enzyme that affect drug metabolism might also extend to changes in formation of bile acids, 25-hydroxyvitamin D₃, or both.

Alternatively, a member of the CYP2A instead of the CYP2D subfamily might have taken on the part played by porcine CYP2D25. CYP2A4 has been shown to be a 25-hydroxylase and 26-hydroxylase of 5α-cholestan-3α,7α,12α-triol and of 25α,26α,27α-trihydroxycholesterol, 24S-hydroxylase, and 27-hydroxylase of 5α-cholestan-3α,7α,12α,25-tetrol; in mice the equivalent CYP2A activity and mRNA are increased in Cyp2a11(−/−) knockout animals.⁸ No increase in liver microsomal CYP2A4 activity was seen in a patient with cerebrotendinous xanthomatosis, suggesting that this species difference explains why the Cyp2a11(−/−) knockout mouse does not show signs and symptoms of cerebrotendinous xanthomatosis. Therefore, in figure 2 and figure 4 we have included both CYP2A4 and (CYP2D6) as possible participants, along with CYP27A1, in the hydroxylations of 25, 26, 27α, 25β, 24α, and 26 in the bile-acid pathway, and in the 25-hydroxylation of colecalciferol.

The CYP27B1 enzyme catalyses 1α-hydroxylation of 25-hydroxy-vitamin D₃ to form the vitamin D₃ receptor (figure 4). Mutations in CYP27B1 encoding this mitochondrial P450 underlie vitamin D-dependent rickets type 1.⁹ The 24-hydroxylation of vitamin D₃ and its intermediates, which is catalysed by the mitochondrial CYP24A1 enzyme, prevents the ligand's subsequent binding to the receptor, and represents the major catabolic pathway of vitamin D₃. Transcription from the human CYP24A1 gene is increased by calcium ions and by excess amounts of 1α,25-dihydroxyvitamin D₃.¹⁰ Defects in the mouse Cyp24a1 gene lead to a nullisence vitamin D₃ and an associated hypervitaminosis D phenotype (panel 2).

Retinol acid hydroxylation

The CYP26 gene family has three genes, one in each of three subfamilies, suggesting that these genes arose from a common ancestor at least 150-200 million years ago. All three catalyse hydroxylation of retinolic acid (vitamin A). CYP26A1 is an all-trans-retinolic acid hydroxylase that does not act on 9-cis or 13-cis retinolic acid. Retinolic acid is an important morphogen during vertebrate development, operating via several retinolic acid receptors and retinoid X receptors.¹¹ As is true of many cytochromes P450 and other drug-metabolizing enzymes, CYP26A1 might catalyse the degradation of the ligand for these retinolic acid receptors, and thus turn off the powerful developmental signals sent by retinoids. CYP26B1 and CYP26C1 also seem to have a role in metabolism of retinolic acid or its derivatives, but the biological parts played by these enzymes have not yet been elucidated.

Cytochrome P450 enzymes of unknown function

Functions of several cytochromes P450—including CYP20A1, CYP27C1, CYP4A20, CYP4F11, CYP4F12, CYP4F23, CYP4V2, CYP4X1, CYP26B1, and CYP26C1—enzymes are unknown or, at best, sketchy.

![Diagram](image_url)
The death of information associated with these proteins is mainly attributable to their method of identification, which largely concerned database searches of the human genome. Some of these genes may have only very limited tissue-specific or cell-type-specific distributions, be transiently expressed, or both during embryogenesis or fetogenesis.

Looking to the future
As more and more CYP gene products are analysed, it seems highly likely that their roles in diverse biological systems will expand. Genes in the CYP superfamily are highly polymorphic, as is true of most (if not all) other genes in the human genome, and with P450 genetic differences contributing to interindividual variation in phenotype, with the attendant results for medicine and treatment. In the near future, many more studies are anticipated that will show associations between CYP variant alleles and myriad genetic diseases, environmental toxic effects and cancer, and other complex diseases.

Conflict of interest statement
None declared.

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