

Ph.D. THESIS

INVESTIGATIONS ON TWO MAJOR FACTORS
INVOLVED IN DRUG METABOLISM:
CYTOCHROME P450 2D6 AND P-GLYCOPROTEIN

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Ph.D. Thesis

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1. INTRODUCTION

While more and more effective drugs are available on the market, the incidence of adverse drug reactions (ADRs) was found to be extremely high; over 100,000 hospital patients died in 1994 due to ADRs according to the most recent statistics available. Furthermore, over 2,000,000 hospital patients experienced a serious, though non-fatal, ADRs in that same year. The fatality statistic placed ADRs between the 4th and 6th leading cause of death in 1994 depending on the confidence interval utilized. Using the more conservative estimate, ADRs were ranked ahead of even pneumonia and diabetes as cause of death. In order to prevent or decrease drug-induced adverse events from occurring, it is critical to fully understand the underlying principle and mechanisms leading to ADRs. While the exact percentage of contribution remains unknown, idiosyncratic drug reactions due to genetic causes are a significant factor contributing to the overall occurrence of ADRs. Bearing this in mind, it is very crucial to advance the current state of knowledge of interindividual variability in drug metabolism. Two important factors involved in the metabolism of different drugs are the cytochrome P450 enzymes and the P-glycoprotein.

The biotransformation of certain drugs is classically delineated as occurring in two distinct enzymatic phases, termed Phase I and Phase II. Phase I biotransformation reactions can play a crucial role in drug detoxification. The majority of Phase I reactions are accomplished via a superfamily of enzymes termed Cytochrome P450 (CYPs). There are four known human CYP450 enzyme families, and they account for the vast majority of Phase I xenobiotic metabolism. The vast majority of the biotransformation of xenobiotics is accomplished by the CYP3A4, CYP2D6, CYP2C9, CYP2C19 cytochrome P450 enzymes. It has long been recognized that humans exhibit wide, and occasionally unpredictable,

variability in both Phase I and II drug metabolism capabilities. Sources of variability are diverse and numerous and can be roughly divided into three categories: environmental, physiological, and genetic. The CYP2D subfamily comprises only 2% of human hepatic P450 but is a very important contributor with respect to Phase I drug metabolism. Indeed, cytochrome P450 2D6 (CYP2D6) metabolizes more than 25% of all currently prescribed medications which are metabolically cleared from the body. These drugs belong to different therapeutic classes including antiarrhythmics, tricyclic antidepressants, serotonin-selective reuptake inhibitors, and opioid analgesics. Among the cytochromes P450, CYP2D6 exhibits the greatest degree of genetic polymorphisms and has, consequently, wide inter-individual variability in both expression and function. Over 75 allelic variants have been described to date; however, only a fraction of variants exhibit total loss of enzyme activity. About 3-10% of the Caucasian population exhibit low CYP2D6 activity, and are “poor metabolizers” (PMs). Therefore, it is important to identify the PM subjects prior to administration of potentially toxic therapeutic agents. The genetic basis of the PM phenotype has been well studied; over 50 different mutations in the gene were found. However, more than 98% of the PM genotype can be accounted for five point-mutations and the deletion of the entire gene. Because genotyping alone could not provide complete prediction of the CYP2D6 phenotype in humans, mRNA transcript levels have been explored as a predictive marker for enzyme activity. A highly sensitive assay designed to estimate full-length CYP2D6 mRNA could allow closer estimation of tissue and cellular concentrations of CYP2D6 mRNA capable of translation into functional enzymes. This type of assay would significantly improve our ability to study the variations in expression of the highly polymorphic CYP2D6 gene in human populations. To fully characterize the relationship of genotype, mRNA transcript levels, and protein expression or enzyme activity, evaluation of all three parameters in the same set of liver tissues is required. While recent advances in PCR-based genotyping and

mRNA transcript analyses can accommodate the use of one mg of tissue, measurement of enzyme activity on such limited sample size has been a formidable challenge. The applicability of commonly employed CYP2D6 probes, including dextromethorphan, bufuralol, and metoprolol, is limited by the relatively large amount of liver proteins required to detect product formation with these traditional substrates. A very high turnover substrate is needed to achieve sufficient sensitivity for measurement of CYP2D6 activity in liver biopsy samples. R-568, a first generation calcimimetic, is a very high turnover, specific substrate of CYP2D6 that fulfills the above criteria. With the added capability to analyze full-length mRNA transcript levels and the availability of a highly sensitive probe for CYP2D6 enzyme activity, it became feasible to evaluate the quantitative relationship between CYP2D6 RNA transcript and enzyme activity in limited mass liver samples. During the experiments we characterized the relationship between CYP2D6 genotype, full-length mRNA transcript level, and *in vitro* O-demethylation rate of R-568 in livers obtained from several patient populations.

Another important factor implied in drug metabolism, P-glycoprotein (Pgp), a member of the ATP-binding cassette family of membrane transporters, is encoded by the human multidrug-resistance (*MDR1*, *ABCB1*) gene. This integral membrane protein functions as an energy-dependent drug efflux pump, and reduces the intracellular concentrations of a wide range of drugs and xenobiotics. including vinca alkaloids, anthracyclines, epipodophyllotoxins, taxols, actinomycin D, cardiac glycosides, immunosuppressive agents, glucocorticoids and anti-HIV protease inhibitors. Since many drugs are substrates of Pgp, its degree of expression and functionality directly affects the therapeutic effectiveness of these agents. The *MDR1* gene is located on the long arm of chromosome 7, and consists of a core promoter region and 29 exons. Although widely investigated, the exact genomic size has remained uncertain for the past 16 years. The online databases list *MDR1* gene length to be

between 6.3 kb and 210 kb. The reported gene structure is mainly based on very limited cell specimens. Comparative and validation studies with different human tissues or cells are not yet available in the literature. Evaluation of the overall length of the human *MDR1* gene would be essential, so that detailed gene structure function studies can be performed with confidence. This knowledge can then serve as a reference when investigating mechanisms of drug resistance due to variation in the *MDR1* gene.

The overall goal of this thesis is to elucidate underlying mechanisms and determinants in genetic variations that lead to inter-subject variability for a key drug metabolizing enzyme, the cytochrome P450 2D6, which is involved in the metabolism of drugs belonging to many therapeutic classes; and also to provide some additional information about the genetic background of another crucial drug mediator efflux pump, the P-glycoprotein (Pgp).

2. SPECIFIC AIMS

The aim of the study is to perform investigations on two important factors that have high influence on drug response: one of the most important human cytochrome P450 enzymes, CYP2D6, and an important cellular efflux transporter, the P-glycoprotein.

In order to achieve our goals we sought

1. To develop a new, easy-to-perform analytical method to assess CYP2D6 full-length messenger RNA levels
2. To compare this full-length mRNA method with short-fragment real-time PCR
3. To perform CYP2D6 genotyping for the most common alleles of different groups of human liver samples
4. To determine the CYP2D6 activity of different human liver tissues with a novel CYP2D6 substrate with improved sensitivity

5. To elucidate the relationship of CYP2D6 ribonucleic acid transcript levels, genotype and enzyme activity in human liver biopsy samples
6. To evaluate and validate the overall length of the human MDR1 gene with different human tissues that will be of great utility for further analyses of drug-induced resistance

3. MATERIALS AND METHODS

The liver samples were collected under four different conditions as described below and grouped accordingly as control subjects—Group I, liver biopsy subjects—Group II, liver transplant subjects—Group III, and liver bank subjects—Group IV. The human lymphocytes were isolated from blood obtained from the Blood Bank. Human cell lines [Messa Dox (ovarian carcinoma), CaCo2 (colon carcinoma) and UW 228 (medulloblastoma)] were purchased from American Type Culture Collection.

The incubations with R-568 and dextromethorphan were analyzed by liquid chromatography-mass spectrometry (LC-MS). *In vitro* enzymatic activity data were analyzed with a two-tailed t-test assuming unequal variances. A P-value of 0.05 or less was considered statistically significant.

DNA was extracted from liver tissue (control population, liver bank, and transplant subjects) and lymphocytes (liver biopsy subjects) with the use of the Qiagen DNeasy Tissue Kit (Qiagen Inc., Valencia CA) according to the manufacturer's instructions. Genotyping was carried out for the most common CYP2D6 variant alleles. Alleles assessed were *3, *4, *5, *6, *7, and *8.

Total RNA was isolated from liver samples using the Totally RNA Isolation Kit (Ambion Inc, Austin TX) and quantitated fluorimetrically. The RT-PCR standard was

developed with the use of a CYP2D6 plasmid kindly supplied by Dr. Frank Gonzalez (NIH, Bethesda, MD). This pUC19 plasmid contains the full-length human CYP2D6 cDNA. A 475 bp deletion in the CYP2D6 gene internal to the start and stop codons, was created by digesting the plasmid in the presence of *Stu*I (Promega, Madison WI) according to the manufacturer's instructions. The truncated linear DNA was then ligated to re-form the circular plasmid. The internally deleted gene fragment was subsequently amplified from the vector via PCR, purified, and cloned into a new vector pSP73 (Promega, Madison, WI). This vector contains the T7 promoter that permits *in vitro* RNA transcription. RNA transcripts of the CYP2D6 gene and internally deleted gene (Δ 2D6) were created by linearizing the full-length and truncated pSP73 plasmids followed by *in vitro* RNA transcription. To estimate CYP2D6 concentration in each liver sample, total RNA (0.5 to 2.0 μ g) was used as template to perform an initial RT-PCR in the absence of the internal control. The RT-PCR products were subjected to 1% agarose gel stained with ethidium bromide, and according to the intensity of the band, we estimated and made serial (3- to 5-fold) dilutions of total RNA. We then used these dilutions in the presence of a fixed copy number of the competitor and determined CYP2D6 copy number.

The quantitation of short RNA transcripts of CYP2D6 with a real-time quantitative RT-PCR method were performed on TaqMan PCR (ABI 7900, Foster City, CA).

For the Southern Blot experiments 10 μ g of genomic DNA was digested to completion with the restriction endonuclease pairs *Bam*HI/*Pac*I and *Bam*HI/*Kpn*I obtained from New England Biolabs (Beverly, MA). The DNA was electrophoresed on a 0.8% agarose gel, transferred to a nitrocellulose membrane and hybridized with ^{32} P-labeled probes prepared by random primed incorporation of α^{32} P-dATP by Klenow DNA polymerase (New England Biolabs, Beverly, MA).

4. RESULTS

Total RNA isolated from human liver samples was subjected to competitive semi-quantitative RT-PCR in the presence of a known copy number of the internal standard. The dilution of total RNA which yielded equivalent signals of native CYP2D6 and Δ 2D6 internal standard was used to calculate the number of CYP2D6 mRNA transcripts present in the original liver sample. The limit of detection for liver RNA is approximately 2500 copies/ μ g.

We next characterized the relationship between mRNA copy number and CYP2D6 enzymatic activity. We compared the ratio of 2D6 full-length transcript number to activity measured *in vitro* as a preliminary attempt to probe the relationship between RNA transcript and enzyme activity. Our results showed that this ratio is relatively constant (0.59 ± 0.09) for the four wild type livers. In contrast, for the same livers the ratio for short fragment of CYP2D6 by Q-RT-PCR showed high variation (2.79 ± 1.75). We analyzed each of the human liver samples for its CYP2D6 genotype with a PCR method. The samples were grouped according to the patient characteristics and how the samples were obtained.

Overall, the subjects ranged in age from 7 to 76 years. There was an approximately even representation of gender across groups, and the majority of subjects were Caucasian. The control group (n=11) was composed mostly of patients being treated for abdominal cancer without hepatic involvement; all had histologically normal livers. These samples were collected during abdominal laparoscopy after obtaining their written consent. The liver biopsy group was comprised mainly of patients diagnosed with chronic hepatitis C, and all subjects underwent this procedure as part of their clinical care (n=21). It should be noted that recovered biopsy masses were very small for this population with a mean mass of less than 6 mg, only less than 1-2 mg of which was available for experiments described in this report. The biopsies obtained from the liver transplant population were collected immediately following re-perfusion of the newly implanted liver (n=11). The Liver Bank samples were

obtained from donor livers that were rejected for transplantation for a variety of reasons. With respect to the genotypes we found in this study, the *4 variant had an overall allelic frequency of approximately 32.7 %, which agrees well with larger population studies.

We determined the copy number for the full-length CYP2D6 transcript in liver for each subject. There were approximately two orders of magnitude of variation in message level across all populations in those subjects having measurable levels of mRNA. CYP2D6 activity was measured using liver homogenates instead of microsomes to conserve samples. With liver homogenates, we were able to perform all incubations and LC-MS experiments in triplicate, and still have tissue left over for RNA extraction and analyses. We compared the R-568 and dextrometphorphan metabolism in human liver homogenates, and found an excellent correlation with an r^2 of 0.94. The mean CYP2D6 activities for each subject population are shown in Figure 1. When comparing CYP2D6 activity among the subjects in the Liver Biopsy group, it appears CYP2D6 activity is affected by severe liver disease, though we found no direct correlation between the Batts & Ludwig score and enzyme activity among this population. However, the overall enzyme activity of this group was statistically different from the control population ($p < 0.005$). Taken together, these data indicate that serious liver disease did affect CYP2D6 activity in these samples.

We examined the relationship between CYP2D6 mRNA copy number and *in vitro* enzymatic activity for the four sets of livers.

The ratio of mRNA copy number-to- enzymatic activity was consistent for the subjects within each group, but varies up to 10-fold across the four test groups. Most notably, the control group exhibited a lower mean ratio compared to the other groups. The data for the control population was subjected to regression analysis to determine the relationship between mRNA copy number and enzyme activity. For this analysis, we only included the subjects with two functional alleles (Figure 2, p value = 0.032). Interestingly, the Control group was

the only population with a fair degree of correlation ($r^2 = 0.54$). If we consider subject 1 as an outlier and omit it from the regression analysis, the r^2 becomes 0.93.

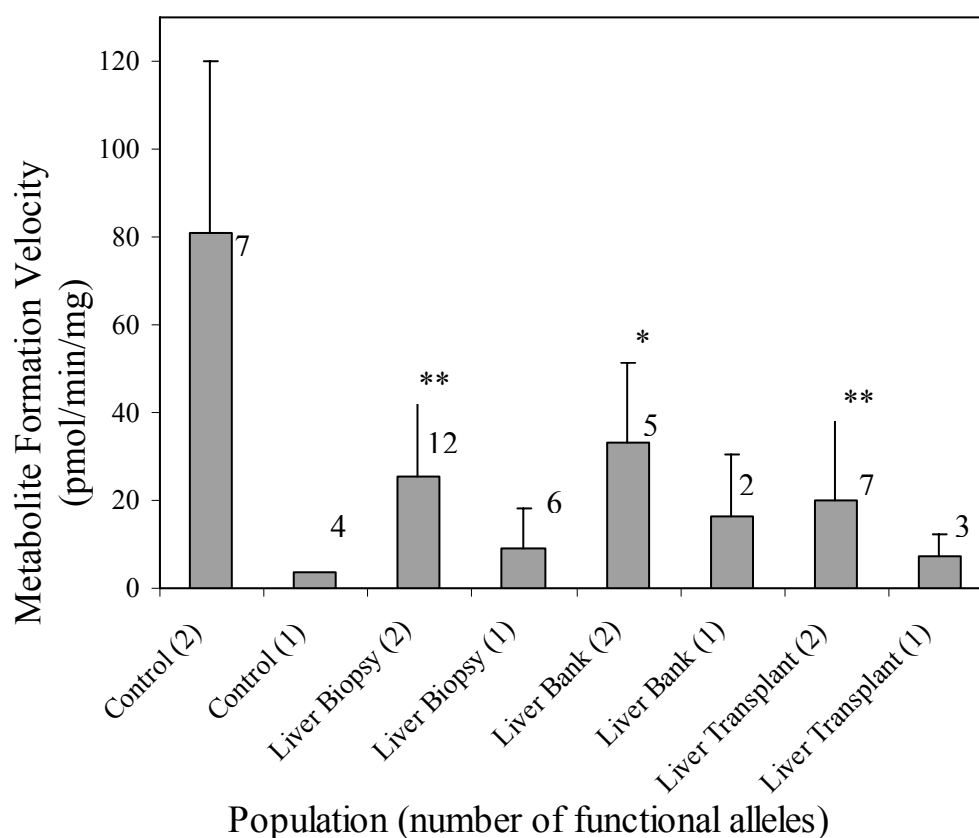


Figure 1. Comparison of hepatic CYP2D6 activity in liver homogenates between the four test population by genotype. The number of functional alleles is given in parentheses for each group. The number of subjects for each column is listed in the figure. * $p < 0.05$, ** $p < 0.005$ relative to control population with two functional alleles.

For the PCR analysis of the of *MDR1* gene we have chosen a critical region (spanning exons 8-21; 43 kb) which would distinguish the 6.3 versus 209 kb version of *MDR1* gene for detailed analysis. To do so, we isolated DNA from liver samples, continuous cell lines expressing Pgp, (Messa Dox - ovarian carcinoma, CaCo2 - colon carcinoma, and UW 228 - primary human medulloblastoma cells), and human lymphocytes. These DNA samples were analyzed with three regions of the *MDR1* gene and used three different primer sets to amplify the respective gene sequences by PCR to distinguish the two versions of *MDR1*.

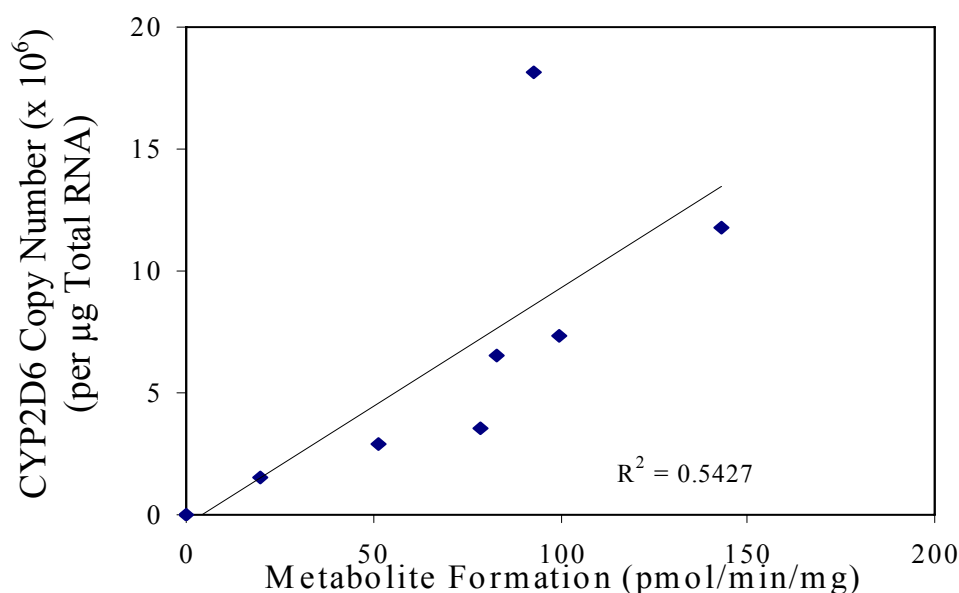


Figure 2. Correlation between CYP2D6 mRNA transcript levels and enzyme activity. The data here are from subjects with two functional alleles in the control population. The correlation coefficient increases to 0.93, if the single outlier is omitted from the analysis

We were not able to detect any product in the reactions corresponding to the 6.3 kb *MDR1* candidate sequence. Instead, we found for all the liver tissues, lymphocytes, and cell lines, the PCR products corresponded to the length predicted with a 209 kb *MDR1* sequence. The PCR results were verified further with Southern Blot analysis to probe introns 8 to 21. The bands correspond to the estimates for the more than two hundred kb gene length. Again, there were no DNA bands corresponding to the length (5 and 6 kb) of product predicted by the 6.3 kb total gene size.

5. DISCUSSION

One of our goals of was to develop an analytical tool to assess cytochrome P450 2D6 levels in the form of full-length transcripts. While a number of strategies have been described for detecting short fragments of CYP2D6 RNA, including those designed for Q-RT-PCR, there was none reported on full-length transcript analysis. We have, for the first time,

successfully developed an assay that detects a full transcript of CYP2D6 RNA. Our CYP2D6 RNA estimates for human livers are comparable with data available in the literature. Interestingly, we noticed that the short sequence CYP2D6 RNA transcript of the same livers estimated with real-time quantitative RT-PCR (Q-RT-PCR) yielded about three order of magnitude lower numbers. The disparity between short- and long CYP2D6 mRNA estimates requires further study. An important aspect to the current assay design is the detection of the full-length CYP2D6 mRNA transcript. While small fragments are indeed detectable, as noted by previous studies, the detection and quantitation of the full-length message may provide a better predictor of functional CYP2D6 protein. While we have demonstrated the detection and quantitation of full-length CYP2D6 mRNA, it is important to note that the principle used in construction of this assay is adaptable to any number of mRNA transcripts of interest. Furthermore, it is not necessary to restrict the assay to drug metabolizing enzymes such as the CYPs. Employing a novel CYP2D6 probe substrate that exhibits an exquisitely high intrinsic clearance (about 20-fold more sensitive than the overall enzyme detection limit of dextromethorphan) and an RT-PCR assay that allows estimation of the full-length transcript, we have evaluated the mRNA transcript levels, genotype and CYP2D6 activity in human livers belonging to four patient groups. Availability of R-568 to determine CYP2D6 activity has permitted elucidation of the relationship between the full-length CYP2D6 mRNA transcript levels and its *in vitro* enzyme activity in human livers collected under varying conditions. Our data strongly suggest that, under physiological conditions, R-568 is a highly selective and sensitive CYP2D6 probe substrate.

When comparing CYP2D6 activity *across* the four sample populations, there was a statistically significant difference between the liver bank, liver transplant and liver biopsy groups relative to the control group (in subjects presumed to carry two functional alleles). Because liver bank samples were obtained from brain-dead donors whose livers were deemed

not suitable for transplantation, their liver enzymes might be down-regulated for reasons including brain injury, procurement conditions, and fatty infiltration. The donor liver, transplanted into liver transplant subjects, could be at a healthier state than that found in the liver bank samples. However, they may also be subjected to similar conditions described above for liver bank samples, without associated fatty infiltration. When considering the effects of liver disease on the liver biopsy population, it is evident that, even in livers with moderate-to-severe disease, there is no effect on CYP2D6 mRNA transcription level. However, we found about 4-fold lower CYP2D6 activity in these subjects, compared to the Control Group. This observation is consistent with a recent data available in the literature. Overall, a comparison of the CYP2D6 enzyme activity and mRNA transcript reveals that livers with one functional allele express lower activity and decreased levels of mRNA compared to those with two functional alleles. The tissue concentration range of CYP2D6 mRNA transcripts reported in the current study was similar in magnitude to that observed by others. When making a comparison of copy number across populations with two functional alleles, only the liver transplant group has lower levels of CYP2D6 mRNA transcripts than the control group. The ratios between CYP2D6 mRNA transcript levels and *in vitro* enzyme activity represent an indirect measure of translation of the transcripts into CYP2D6 protein as reflected in enzyme activity. If translation of CYP2D6 mRNA is closely regulated, the ratio of the two measures would be relatively constant across all subjects. Our results showed that *within* each test group mRNA transcripts-to-activity ratio remained relatively constant. When comparing the activity-to-mRNA transcript ratio across groups, the mean ratio is much higher for the control group relative to the others. The higher enzyme activity content per copy of transcript may signify more efficient translation to CYP2D6 proteins and/or slower turnover of CYP2D6 protein. The cause for the ratio discordance may be multifactorial. It is possible that these liver biopsies are from healthier individuals without any of the pathology or

collection damage associated with the other groups, including fatty infiltration, liver disease or ischemia, thus leading to CYP2D6 with higher catalytic efficiency or diminished degradation of protein. However, the relatively constant activity-to-mRNA transcript ratio within the control population indicates that quantitation of the full-length mRNA transcript may be predictive of both *in vitro* and *in vivo* CYP2D6 function, particularly for those liver samples collected under conditions that preserve enzymatic and RNA integrity. It is noteworthy that the relationship holds true for livers with two functional alleles and is somewhat less clear for livers with only one functional allele.

We have presented the inter-relationships between CYP2D6 genotype, mRNA transcript, and *in vitro* liver enzyme activity. The detection and quantitation of the full-length CYP2D6 transcript is an improved technique to monitor mRNA transcripts as truncated message fragments are not translated into CYP2D6 protein. The data from this study indicate that mRNA level is well-correlated to *in vitro* enzymatic activity for liver samples obtained from healthy individuals with two functional alleles.

Another goal of our investigations was to determine the MDR1 gene length by PCR and Southern Blot experiments using different human tissue samples and cell cultures. As the Genbank data are often based on the analysis of limited DNA specimens, we used several different human cell lines as well as lymphocyte and liver samples to investigate eventual differences between tissues and/or subjects regarding the *MDR1* gene locus. Both sets of experiments confirm the length of the *MDR1* gene being much longer than 6.3 kb, and it is most likely 209 kb as indicated in the database. The results were consistent in the cases of different human liver tissue samples, several cell lines and lymphocytes, showing that there is very little, if any, interindividual variation with respect to the gene length. The results of our study confirming the size of the *MDR1* gene will be of great utility when extended to analyses of mechanisms of drug-induced resistance. In other words, knowledge of both intron-exon

structure and overall gene length can be used to differentiate between aberrant mRNA splicing and gene deletions in multidrug resistance.

6. SUMMARY

We have developed an efficient and reliable assay to detect and quantitate full-length 1.5 kb CYP2D6 mRNA transcripts from any tissue or cell source. The CYP2D6 activity appeared to relate more closely to full-length CYP2D6 mRNA concentration than a short-sequence of CYP2D6 RNA estimated with a real-time quantitative RT-PCR assay. This assay could be adapted to detect other mRNA transcripts of interest.

The CYP2D6 activity in tissue homogenates of liver biopsy specimens collected from control subjects (with no apparent liver disease), liver biopsy subjects, liver transplant subjects, and liver bank specimens were assessed with a newly developed and validated a CYP2D6 probe substrate, R-568, that offers a 20-fold higher sensitivity than dextromethorphan. The improved assay sensitivity allowed evaluation of CYP2D6 enzyme activity in a few milligrams of tissue collected from biopsy.

The liver samples grouped in four populations were genotyped for the six most common CYP2D6 genetic variants (i.e., *3, *4, *5, *6, *7 and *8). The overall allelic frequency agreed well with data available in the literature. A combination of genotyping and mRNA level determination could allow a quantitative estimation of functional CYP2D6 activity in healthy human livers with a reasonable degree of confidence.

Using PCR and Southern Blot techniques with DNA derived from different human cell lines and tissues, we have characterized the *MDR1* genomic sequence and established that the total gene length is likely to be 209 kb.

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